UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ALASKA ELECTRICAL PENSION FUND, et al., Plaintiffs, -against- PHARMACIA CORP., et al., Defendants.	03-CV-1519 (AET)

DECLARATION OF WILLIAM A. DREIER IN SUPPORT OF DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR CLASS CERTIFICATION

Pursuant to 28 U.S.C. § 1746, William A. Dreier declares:

1. I am an attorney admitted to practice before this Court and a member of Norris, McLaughlin & Marcus, PA, counsel for defendants Pharmacia Corporation, Fred Hassan, G. Steven Geis, Carrie Cox, and Pfizer Inc. (collectively "Defendants"). I submit this declaration in support of Defendants' opposition to Plaintiffs' motion for class certification.

2. Attached hereto as Exhibit 1 is a true and correct copy of a September 13, 2000 Journal of the American Medical Association ("JAMA") article entitled *Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis - The CLASS Study: A Randomized Controlled Trial* by Fred E. Silverstein, M.D., *et al.*

3. Attached hereto as Exhibit 2 is a true and correct copy of an April 17, 2000 press release.

4. Attached hereto as Exhibit 3 is a true and correct copy of a transcript of an April 25, 2000 conference call with financial analysts.

5. Attached hereto as Exhibit 4 is a true and correct copy of an April 17, 2000 Dow Jones News Service article entitled *Pfizer/Pharmacia Arthritis Product Effective in Study*.

6. Attached hereto as Exhibit 5 is a true and correct copy of an April 17, 2000 Dow Jones News Service article entitled *Pharmacia-Pfizer Study Underscores Celebrex Safety* by Beth M. Mantz.

7. Attached hereto as Exhibit 6 is a true and correct copy of an April 17, 2000 J.P. Morgan Securities Inc. analyst report entitled *Celebrex CLASS Trial Confirms G.I. Safety (With a Slight Wrinkle) - No Cardiovascular Risk.*

8. Attached hereto as Exhibit 7 is a true and correct copy of an April 24, 2000 "The Pink Sheet" article entitled *Searle To Discuss Adding Celebrex 13-Month Safety Data To Label With FDA*.

9. Attached hereto as Exhibit 8 is a true and correct copy of a May 23, 2000 press release.

10. Attached hereto as Exhibit 9 is a true and correct copy of the Briefing Document submitted to the United States Food and Drug Administration (the "FDA") Arthritis Advisory Committee, dated February 7, 2001.

11. Attached hereto as Exhibit 10 is a true and correct copy of *Medical Officer's Gastroenterology Advisory Committee Briefing Document* by Lawrence Goldkind, M.D.

12. Attached hereto as Exhibit 11 is a true and correct copy of *Medical Officer Review* by James Witter, M.D., Ph.D.

13. Attached hereto as Exhibit 12 is a true and correct copy of *Statistical Reviewer Briefing Document for the Advisory Committee* by Hong Laura Lu, Ph.D.

14. Attached hereto as Exhibit 13 is a true and correct copy of an April 12, 2001 FDA Department of Health and Human Services "approvable letter."

15. Attached hereto as Exhibit 14 is a true and correct copy of a June 7, 2002 Credit Suisse First Boston analyst report entitled *FDA Approves Celebrex Improved Gastrointestinal Safety Labeling.*

16. Attached hereto as Exhibit 15 is a true and correct copy of a February 7, 2001 J.P. Morgan Securities analyst report entitled *FDA Review of Celebrex More Negative Than Expected – Panel Could Be Controversial.*

17. Attached hereto as Exhibit 16 is a true and correct copy of pages 1 and 2 of a February 6, 2001 Bloomberg newswire report entitled *Pharmacia Hasn't Shown Celebrex Safety Benefit, FDA Review Says* by Brian Reid.

18. Attached hereto as Exhibit 17 is a true and correct copy of excerpts from the transcript of the February 7, 2001 FDA Arthritis Advisory Committee Hearing.

19. Attached hereto as Exhibit 18 is a true and correct copy of a June 7, 2002 Department of Health and Human Services Food and Drug Administration "FDA Talk Paper" entitled *Labeling Changes for Arthritis Drug Celebrex.*

20. Attached hereto as Exhibit 19 is a true and correct copy of a February 8, 2001 *Chicago Tribune* article entitled *Tests Fail To Show Celebrex Drug Safer Than Rivals.*

21. Attached hereto as Exhibit 20 is a true and correct copy of a February 8, 2001 Merrill Lynch analyst report entitled *CLASS Trial – Something Ventured, Nothing Gained.*

22. Attached hereto as Exhibit 21 are true and correct copies of November 21, 2001 Letters to the Editor of JAMA submitted by (i) Jennifer Berg Hrachovec, PharmD, M.P.H. and Marc Mora, M.D. and (ii) James M. Wright, M.D., Ph.D., *et al.*, published under the heading "Reporting of 6-Month vs 12-Month Data in a Clinical Trial of Celecoxib," and an "In Reply" submitted by Fred Silverstein, M.D., *et al.*

23. Attached hereto as Exhibit 22 is a true and correct copy of a November 12, 2002 Canadian Medical Association Journal article entitled *The Double-Edged Sword Of Cox-2 Selective NSAIDs* by Dr. James M. Wright.

24. Attached hereto as Exhibit 23 is a true and correct copy of an August 5, 2001 Washington Post article entitled *Missing Data on Celebrex - Full Study Altered Picture of Drug* by Susan Okie.

25. Attached hereto as Exhibit 24 is a true and correct copy of a September 2002 Canadian Family Physician article entitled *Cyclooxygenase-2 Inhibitor Update - Journal Articles Fail To Tell The Full Story* by Ken Bassett, M.D., Ph.D, *et al.*

26. Attached hereto as Exhibit 25 is a true and correct copy of an August 22, 2001 Wall Street Journal article entitled *Note Of Caution: Study Raises Specter Of Cardiovascular Risk For Hot Arthritis Pills* by Thomas M. Burton and Gardiner Harris.

27. Attached hereto as Exhibit 26 is a true and correct copy of a June 1, 2002 British Medical Journal editorial entitled *Are Selective Cox-2 Inhibitors Superior To Traditional Non Steroidal Anti-Inflammatory Drugs? – Adequate Analysis Of The CLASS Trial Indicates That This May Not Be The Case* by Peter Jüni, *et al.*

28. Attached hereto as Exhibit 27 is a true and correct copy of a May 25, 2000 Morgan Stanley Dean Witter analyst rReport entitled *Positive Clinical Outcomes Studies Presented at DDW.*

29. Attached hereto as Exhibit 28 is a true and correct copy of a June 2, 2000 Arnhold and S. Bleichroeder, Inc. analyst report entitled *COX-2 Inhibitor Update.*

30. Attached hereto as Exhibit 29 is a true and correct copy of a June 8, 2000 J.P. Morgan Securities Inc. analyst report entitled *A Low-Risk Ride on the COX-2 Wave.*

31. Attached hereto as Exhibit 30 is a true and correct copy of a February 7, 2001 Salomon Smith Barney analyst report entitled *PHA: FDA Reviews Celebrex & Vioxx.*

32. Attached hereto as Exhibit 31 is a true and correct copy of an April 16, 2001 Lehman Brothers analyst report entitled *Celebrex Approvable Letter . . . Remember the Data!.*

33. Attached hereto as Exhibit 32 is a true and correct copy of a September 13, 2000 JAMA editorial entitled *COX-2-Selective NSAIDs, New And Improved?* by David R. Lichtenstein, M.D. and M. Michael Wolfe, M.D.

34. Attached hereto as Exhibit 33 is a true and correct copy of an April 18, 2000 Morgan Stanley Dean Witter analyst report entitled *Positive Results of Celebrex CLASS Trial Released.*

35. Attached hereto as Exhibit 34 is a true and correct copy of excerpts from the June 8, 2006 deposition of Ted J. Ujazdowski of Ark Asset Management Co.

36. Attached hereto as Exhibit 35 is a true and correct copy of excerpts from the June 27, 2006 deposition of Jane Davenport of Montag & Caldwell.

37. Attached hereto as Exhibit 36 is a true and correct copy of excerpts from the June 19, 2006 deposition of Erick J. Lucera formerly of Independence Investment Associates.

38. Attached hereto as Exhibit 37 is a true and correct copy of excerpts from the June 29, 2006 deposition of David Thompson of Highland Capital Management.

39. Attached hereto as Exhibit 38 is a true and correct copy of excerpts from the May 23, 2006 deposition of Ronald L. Burdette of International Union of Operating Engineers Local 132 Pension Fund.

40. Attached hereto as Exhibit 39 is a true and correct copy of excerpts from the May 18, 2006 deposition of Scott M. Brewer of Chemical Valley Pension Fund.

41. Attached hereto as Exhibit 40 is a true and correct copy of excerpts from the June 21, 2006 deposition of Thomas J. Broom of City of Sarasota Firefighters Pension Fund.

42. Attached hereto as Exhibit 41 is a true and correct copy of excerpts from the June 7, 2006 deposition of Gregory Stokes of Alaska Electrical Pension Fund.

I declare under penalty of perjury that the foregoing is true and correct. Executed on August 30, 2006 in Bridgewater, N.J.

WILLIAM A. DREIER (WD 1158)

EXHIBIT 1

Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

The CLASS Study: A Randomized Controlled Trial

Fred E. Silverstein, MD
Gerald Faich, MD
Jay L. Goldstein, MD
Lee S. Simon, MD
Theodore Pincus, MD
Andrew Whelton, MD
Robert Makuch, PhD
Glenn Eisen, MD
Naurang M. Agrawal, MD
William F. Stenson, MD
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James B. Lefkowith, MD
Kenneth M. Verburg, PhD
C. Steven Geis, PhD, MD

Context Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of inhibition of cyclooxygenase (COX)-1. Whether COX-2–specific inhibitors are associated with fewer clinical GI toxic effects is unknown.

Objective To determine whether celecoxib, a COX-2–specific inhibitor, is associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs.

Design The Celecoxib Long-term Arthritis Safety Study (CLASS), a double-blind, randomized controlled trial conducted from September 1998 to March 2000.

Setting Three hundred eighty-six clinical sites in the United States and Canada.

Participants A total of 8059 patients (≥18 years old) with osteoarthritis (OA) or rheumatoid arthritis (RA) were enrolled in the study, and 7968 received at least 1 dose of study drug. A total of 4573 patients (57%) received treatment for 6 months.

Interventions Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; n=3987); ibuprofen, 800 mg 3 times per day (n=1985); or diclofenac, 75 mg twice per day (n=1996). Aspirin use for cardiovascular prophylaxis (≤325 mg/d) was permitted.

Main Outcome Measures Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.

Results For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% ($P=.09$) and 2.08% vs 3.54% ($P=.02$), respectively. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% ($P=.04$) and 1.40% vs 2.91% ($P=.02$). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% ($P=.92$) and 4.70% vs 6.00% ($P=.49$). Fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use.

Conclusions In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

JAMA. 2000;284:1247-1255 www.jama.com

FOR PATIENTS WITH MUSCULOskeletal disorders, conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care.[1-3] Well-established limitations of NSAID therapy, however, include the risk of developing significant injury to the upper gastrointestinal (GI) tract.[4-10] The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1%-2% for ulcer complications alone).[11-15] NSAID-related ulcer complications are estimated to lead to

For editorial comment see p 1297.

Author Affiliations and Financial Disclosures are listed at the end of this article.
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107 000 hospitalizations and 16 500 deaths yearly in the United States.[10]

NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for conversion of arachidonic acid to prostaglandins.[16] COX exists in 2 isoforms.[17] COX-1 is a ubiquitous constitutive isozyme producing prostaglandins responsible for homeostatic functions such as maintenance of GI mucosal integrity.[17] COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[17] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[18,19] Thus, the therapeutic effects of conventional NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents, particularly in the upper GI tract, arise from inhibition of COX-1 activity.

Celecoxib, a COX-2–specific inhibitor, recently was approved by the US Food and Drug Administration (FDA) for symptomatic treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). To determine whether the COX-2 specificity of celecoxib is associated with lower COX-1–related adverse effects, we compared celecoxib administered at 2 and 4 times the maximum FDA-approved effective dosages for RA and OA, respectively, with commonly used therapeutic dosages of ibuprofen and diclofenac. The dosage of celecoxib exceeded the maximum dosage approved by the FDA for OA and RA to permit a safety assessment of the higher dosages. However, based on previous studies,[20,21] exceeding the dosages approved by the FDA would not improve patients' symptom relief. The dosages of ibuprofen and diclofenac were based on prescription data; 48% and 60% of OA and RA patients, respectively, who received ibuprofen were prescribed a dosage of at least 2400 mg/d, and 36% and 57% of OA and RA patients, respectively, who received diclofenac were prescribed a dosage of at least 150 mg/d.[22]

METHODS

Study Population

Outpatients aged 18 years or older were eligible to participate in the study if, on screening, they were diagnosed as having RA or OA evident for at least 3 months and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from study participation if at screening they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; history of gastric or duodenal surgery other than an oversew; or known immediate-type hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might have become pregnant, or were lactating.

Study Protocol

This prospective, randomized double-blind trial was conducted at 386 centers in the United States and Canada from September 1998 to March 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site, and all patients provided written informed consent. Prior to enrollment, patients completed a physical examination and clinical laboratory testing. After a baseline visit, follow-up clinic visits took place at weeks 4, 13, and 26 after the initial dose of medication, and every 13 weeks thereafter. All patients were provided an opportunity to complete a minimum of 6 months of treatment.

Patients withdrawing from study participation prior to 6 months were classified as follows: preexisting violation of entry criteria, protocol noncompliance (investigator-defined failure to comply with the requirements of the protocol, eg, failure to take at least 70% of the study medication in any 13-week interval), treatment failure (investigator-defined failure of study medication to control arthritis signs and symptoms), or adverse effect (investigator-defined signs or symptoms unrelated to arthritis; see "Clinical Assessments" herein). These patients nonetheless were followed up for end-point evaluation for 2 months or until study termination.

Treatment

Patients were randomly assigned to receive treatments (celecoxib, 400 mg twice per day; ibuprofen, 800 mg 3 times per day; or diclofenac, 75 mg twice per day) on a 2:1:1 basis by an interactive voice response system (ClinPhone, Nottingham, England) according to a computer-generated randomization schedule. All treatment regimens were blinded and double dummy. Treatment assignment for 3 patients was unblinded by study site personnel during trial conduct (1 at the investigation site, 2 via the interactive voice response system). None of these patients experienced a study outcome event. One celecoxib patient experienced diverticular bleeding; 2 patients (1 celecoxib and 1 diclofenac) experienced non–GI-related adverse events; and in no instance was the treatment assignment made known to personnel of the drug company (Pharmacia, Skokie, Ill) or to members of the oversight committees prior to final review of all end points by a GI events committee.

Concomitant Medications

NSAIDs (except for stable dosages of aspirin up to 325 mg/d); antiulcer drugs (except for occasional antacid use); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *Helicobacter pylori* infection; and antineoplastics (except methotrexate or azathioprine for RA) were prohibited during the study. Use of oral, intramuscular, and intra-articular glucocorticoids and disease-modifying antirheumatic drugs was permitted.

Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a prespecified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: hematemesis; melena; acute

hypovolemia/hypotension; development of postural dizziness, lightheadedness, or syncope; history of dark stool, hematochezia, or anal or rectal bleeding; development of new anemia (defined as a hematocrit level outside of the reference range) or a decrease in hematocrit of at least 5 percentage points; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of occult blood-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgment.

All documentation relating to potential ulcer complications was forwarded to a GI events committee (J.L.G., G.E., N.M.A., and W.F.S). The committee collectively reviewed each case in a treatment-blinded fashion and assigned it by unanimous consensus as either meeting or not meeting the definition of an upper GI ulcer complication (TABLE 1). Symptomatic ulcers consisted of cases that did not meet the definition of an ulcer complication but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study and included in the analysis as having had a study end point.

Adverse effect data were collected at each visit (and as reported spontaneously) using the following question: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?" All affirmative responses were recorded regardless of severity or relationship to study drug. Laboratory data were also collected at each visit and as indicated according to the investigators' discretion. Clinically significant changes in hematocrit and hemoglobin were predefined as decreases of at least 10 percentage points and 20 g/L, respectively. Clinically significant changes in serum urea nitrogen and creatinine were predefined as values at 6-month follow-up of at least 40 mg/dL (14.3 mmol/L) and 1.8 mg/dL (159 μmol/L), respectively. Clinically significant changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were predefined as increases to at least 3 times the upper limit of normal. Trial safety (eg, serious adverse effects) was monitored in a treatment-blinded fashion during the study by the data safety monitoring board (G.F., T.P., A.W., and R.M.).

Table 1. Protocol-Specified Definitions and Adjudication Criteria for Ulcer Complications

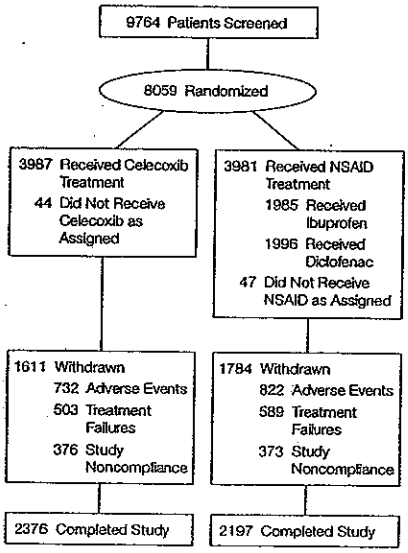
Event	Criteria for Confirmed Event
Gastric or duodenal perforation	Perforated lesion requiring surgery. Could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible on radiograph or peritoneal signs on physical examination.
Gastric outlet obstruction	Gastric outlet obstruction requiring diagnosis by investigator; diagnosis was required to be supported by endoscopy (eg, ulcer with a tight edematous pyloric channel) or by radiographic results (eg, dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, severe outlet narrowing and edema)
Upper gastrointestinal bleeding	Hematemesis with a lesion (ulcer or large erosion) on endoscopy or radiograph Lesion (ulcer or large erosion) on endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer) Melena with a lesion (ulcer or large erosion) on endoscopy or radiograph Occult blood-positive stool with a lesion (ulcer or large erosion) on endoscopy or radiograph and with evidence of serious bleeding, including at least 1 of the following: Decrease from baseline in hematocrit of ≥5 percentage points or in hemoglobin of >15 g/L Postural vital sign changes (increase in heart rate of ≥20/min and/or decrease in systolic blood pressure of ≥20 mm Hg and/or in diastolic blood pressure of ≥10 mm Hg) Transfusion of ≥2 units of blood Blood in stomach on endoscopy or nasogastric aspiration

Statistical Analysis

Sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect this difference with a 2-sided .05 significance level with statistical power of 85% and assuming a 35% withdrawal rate, a sample size of approximately 4000 patients was required for the celecoxib group and 2000 patients were needed for each of the 2 NSAID groups.

Homogeneity of the treatment groups at baseline was analyzed using the χ^2 test for categorical data and 2-way analysis of variance with treatment and center effects for continuous-valued data. Statistical analyses were conducted on the intent-to-treat population, defined a priori in the protocol as consisting of all patients who received at least 1 dose of assigned study medication. An additional prespecified analysis was performed on the population of patients not taking aspirin (since aspirin use was a predefined risk factor for GI events). Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on cumulative event rates (symptomatic ulcers and/or ulcer complications) for the 6-month study period and are expressed as annualized incidence rates (number of events per 100 patient-years of exposure or percentage). The log-rank test was used to compare time-to-event curves among treatment groups. Based on the recommendation of the GI events committee and as specified by the protocol a priori, upper GI ulcer complications were defined as a study end point (ie, an uncensored event) if they occurred within the 6-month treatment period and occurred 48 hours after the first dose day or before 14 days after the last known dose of study drug (to avoid confounding due to prestudy or poststudy NSAID use). Patients who had upper GI ulcer complications outside of the specified

Figure 1. Flowchart of Patient Disposition at 6 Months



time frame were censored for purposes of time-to-event analysis. This recommendation was based on the pharmacologic washout period for most common NSAIDs and evidence in the literature of carryover effects of NSAIDs in terms of GI toxic effects.[8,23] Analyses were conducted with and without these censored patients. The effects of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were analyzed by Cox proportional hazards models. The incidences of treatment-emergent adverse effects or clinical laboratory changes in the different treatment groups during the 6 months were compared using the Fisher exact test. All *P* values and 95% confidence intervals (CIs) are 2-sided. No significant differences in adverse events were noted by sex, so results are presented with women and men combined. Adverse events for diclofenac and ibuprofen were similar except for liver enzyme elevations, for which results are presented separately.

RESULTS

A total of 8059 patients were randomized (FIGURE 1). Ninety-one patients did not receive study drug (32 were randomized and found to be ineligible prior to administration of study drug; 59 withdrew consent prior to taking study drug). Of these 91 patients, 44 were randomized to celecoxib and 47 were randomized to NSAIDs.

A total of 7968 patients received at least 1 dose of medication. Of these, 3987 patients were treated with celecoxib, 400 mg twice per day, and 3981 patients were treated with NSAIDs (1985 received ibuprofen, 800 mg 3 times per day, and 1996 received diclofenac, 75 mg twice per day). The celecoxib and NSAID groups had 1441 and 1384 total patient-years of exposure, respectively. Baseline characteristics did not differ significantly between groups (TABLE 2). More than 20% of the patients were taking low-dosage aspirin (≤325 mg/d). Approximately 57% of the patients (n=4573) completed 6 months of treatment (Figure 1). More patients in the NSAID treatment group withdrew from the study for either adverse effects (n=822 [20.6%]) or lack of therapeutic efficacy (n=589 [14.8%]) than did celecoxib-treated patients (n=732 [18.4%] and n=503 [12.6%], respectively; *P*=.01 and *P*=.005; Figure 1). No patients were lost to follow-up (ie, a cause of withdrawal was determined for all patients who withdrew).

Table 2. Baseline Patient Characteristics*

Characteristics	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)
Age, mean (range), y	60.6 (20-89)	59.8 (18-90)
>65 y, %	39.1	37.3
>75 y, %	12.2	11.4
Women, %	68.5	69.1
Race/ethnicity, %		
White	88.5	87.9
Black	7.5	8.2
Hispanic	2.7	2.8
Asian	0.7	0.8
Other	0.6	0.6
Primary rheumatoid arthritis, %	27.3	27.5
Duration of disease, mean (SD), y		
Osteoarthritis	10.3 (9.7)	10.1 (9.9)
Rheumatoid arthritis	11.3 (9.9)	10.7 (9.6)
NSAID therapy at study entry, %	81.4	81.6
Ibuprofen	21.7	20.9
Diclofenac	13.6	14.0
Potential risk factor, %		
History of gastrointestinal bleeding	1.7	1.5
History of gastrointestinal ulcer	8.4	8.1
Helicobacter pylori infection, %	38.5	38.2
Tobacco use, %	15.8	14.9
Alcohol use, %	30.9	30.1
Concurrent medications, %		
Aspirin (≤325 mg/d)	20.9	20.4
Corticosteroids	30.6	29.5
Anticoagulants	1.1	1.1

*NSAID indicates nonsteroidal anti-inflammatory drug.

GI Toxicity

A total of 260 cases were selected by the GI events committee for adjudication. The committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic but uncomplicated gastroduodenal ulcers (TABLE 3). Four upper GI ulcer complications (2 in celecoxib-treated patients and 2 in NSAID-treated patients) were censored according to predetermined criteria (see "Methods" section). The remaining 177 cases not meeting the definition of gastroduodenal ulcer or ulcer

complication were assigned a diagnosis from the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients was 0.76% (11 events/1441 patient-years) vs an incidence of 1.45% (20 events/1384 patient-years) for patients taking NSAIDs ($P=.09$; FIGURE 2A). The relative risk (RR) for celecoxib compared with NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was 2.08% (30 events/1441 patient-years) vs 3.54% (49 events/1384 patient-years) for patients taking NSAIDs ($P=.02$; Figure 2A). The RR for celecoxib compared with NSAIDs was 0.59 (95% CI, 0.38-0.94).

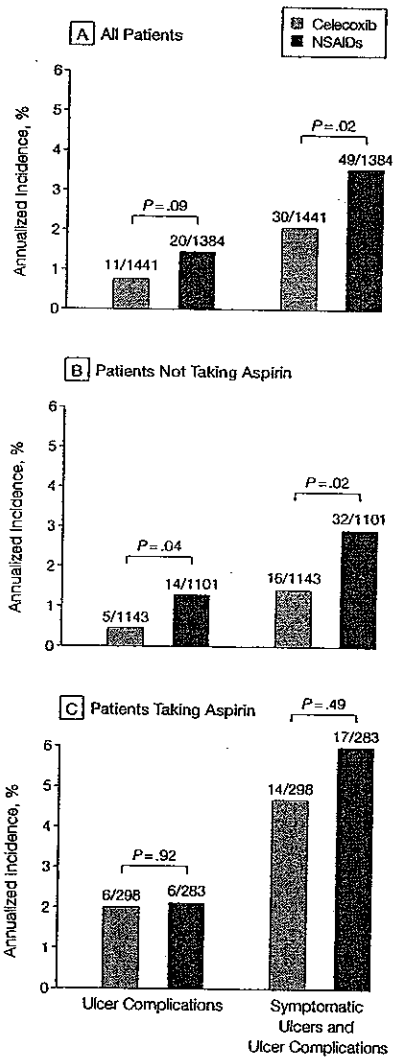
Inclusion of the 2 censored events in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.90% (13 events/1441 patient-years) and 1.59% (22 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P=.11$). For upper GI ulcer complications plus symptomatic ulcers, the rates were 2.22% (32 events/1441 patient-years) and 3.68% (51 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P=.03$). Corticosteroid use was not significantly associated with the incidence of upper GI ulcer complications in either treatment group (RR, 0.2 and 0.6 for patients treated with celecoxib and NSAIDs, respectively; $P=.13$ and $P=.27$).

GI Toxicity With Aspirin Use

Based on time-to-event analyses using a Cox proportional hazard model, low-dosage aspirin use was found to have a significant effect on the incidence of upper GI ulcer complications in celecoxib-treated patients. Within the celecoxib treatment group, the RR of an upper GI ulcer complication was 4.5 with low-dosage aspirin use: 6 events in 833 patients taking low-dosage aspirin vs 5 events in 3154 non–aspirin users ($P=.01$). Low-dosage aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (RR, 1.7; $P=.29$).

When the non–aspirin-using cohort was examined, 2 upper GI ulcer complications were censored (1 in each group). The annualized incidence of upper GI ulcer complications in non–aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% [5 events/1143 patient-years] vs 1.27% [14 events/1101 patient-years]; $P=.04$; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence

Figure 2. Annualized Incidence of Upper Gastrointestinal Tract Ulcer Complications Alone and With Symptomatic Gastroduodenal Ulcers



Numbers above bars indicate events per patient-years of exposure. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

Table 3. Adjudicated Cases Meeting and Not Meeting Prespecialized Definitions of Gastroduodenal Ulcers and Ulcer Complications*

	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)
Total No. of cases adjudicated	111	149†
No. of adjudicated cases not meeting the definition of a gastroduodenal ulcer or ulcer complication		
Esophageal disease	23	21
Gastroduodenitis	12	21
Colonic or small bowel disease	10	7
Nonulcer bleeding	10	17
Miscellaneous GI symptoms	18	20
Anemia	5	12
Cholelithiasis	1	0
Total	79	98
No. of adjudicated cases meeting the definition of a gastroduodenal ulcer or ulcer complication		
Gastroduodenal ulcers	19	29
Ulcer complications‡	13	22
Upper GI bleeding	10	20
Perforation	0	0
Gastric outlet obstruction	1	0
Total	32	51

*NSAID indicates nonsteroidal anti-inflammatory drug; GI, gastrointestinal.
†$P<.001$ vs celecoxib group.
‡Four ulcer complications (2 in the celecoxib group and 2 in the NSAID group) were censored from the analysis because of the timing of the event based on a priori–specified definitions.

of upper GI ulcer complications plus symptomatic ulcers in patients not taking aspirin was also significantly lower with celecoxib than with NSAIDs (1.40% [16 events/1143 patient-years] vs 2.91% [32 events/1101 patient-years]; $P=.02$; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.48 (95% CI, 0.28-0.89).

Inclusion of the 1 censored event in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.52% (6 events/1143 patient-years) and 1.36% (15 events/1101 patient-years) for celecoxib and NSAIDs, respectively ($P=.05$). For upper GI ulcer complications plus symptomatic ulcers, the rates were 1.49% (17 events/1143 patient-years) and 3.00% (33 events/1101 patient-years) for celecoxib and NSAIDs, respectively ($P=.02$).

Table 4. Adverse Effects During the 6-Month Treatment Period*

Adverse Effects	All Patients		Patients Not Taking Aspirin	
	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)	Celecoxib Group (n = 3154)	NSAID Group (n = 3169)
Gastrointestinal				
Dyspepsia	575 (14.4)	640 (16.1)†	427 (13.5)	496 (15.7)†
Abdominal pain	387 (9.7)	522 (13.1)†	286 (9.1)	395 (12.5)†
Diarrhea	373 (9.4)	392 (9.8)	288 (9.1)	293 (9.2)
Nausea	277 (6.9)	370 (9.3)†	213 (6.8)	277 (8.7)†
Constipation	68 (1.7)	234 (5.9)†	48 (1.5)	172 (5.4)†
Total	**1250** (31.4)	**1465** (36.8)†	**942** (29.9)	**1127** (35.6)†
Withdrawals	345 (8.7)	427 (10.7)†	252 (8.0)	321 (10.1)†
Hepatic				
Elevated serum ALT	23 (0.6)	88 (2.2)†	18 (0.6)	68 (2.1)†
Elevated serum AST	18 (0.5)	73 (1.8)†	13 (0.4)	60 (1.9)†
Total	24 (0.6)	**93** (2.3)†	**18** (0.6)	**72** (2.3)†
Withdrawals	2 (<0.1)	46 (1.2)†	2 (<0.1)	36 (1.1)†
Bleeding-related				
Anemia	81 (2.0)	175 (4.4)†	59 (1.9)	123 (3.9)†
Ecchymosis	28 (0.7)	32 (0.8)	22 (0.7)	26 (0.8)
Hematochezia	17 (0.4)	40 (1.0)†	11 (0.3)	29 (0.9)†
Total	**123** (3.1)	**238** (6.0)†	**90** (2.9)	**171** (5.4)†
Withdrawals	16 (0.4)	26 (0.7)	13 (0.4)	19 (0.6)
Renal				
Peripheral edema	113 (2.8)	138 (3.5)	90 (2.9)	108 (3.4)
Hypertension	66 (1.7)	90 (2.3)†	50 (1.6)	65 (2.1)
Increased creatinine level	28 (0.7)	48 (1.2)†	20 (0.6)	33 (1.0)
Total	200 (5.0)	263 (6.6)†	**155** (4.9)	**198** (6.2)†
Withdrawals	44 (1.1)	41 (1.0)	37 (1.2)	32 (1.0)
Cardiovascular				
Cerebrovascular accident	5 (0.1)	10 (0.3)	3 (<0.1)	5 (0.2)
Myocardial infarction	10 (0.3)	11 (0.3)	3 (<0.1)	4 (0.1)
Angina	24 (0.6)	22 (0.6)	10 (0.3)	7 (0.2)
Total	37 (0.9)	39 (1.0)	**16** (0.5)	**14** (0.4)
Withdrawals	12 (0.3)	13 (0.3)	9 (0.3)	5 (0.2)
Cutaneous				
Rash	218 (5.5)	103 (2.6)†	180 (5.7)	91 (2.9)†
Pruritus	91 (2.3)	59 (1.5)†	72 (2.3)	44 (1.4)†
Urticaria	22 (0.6)	14 (0.4)	18 (0.6)	13 (0.4)
Total	**298** (7.5)	**163** (4.1)†	**241** (7.6)	**136** (4.3)†
Withdrawals	109 (2.7)	49 (1.2)†	92 (2.9)	43 (1.4)†

*Data are given as No. (%) of patients. Categories are nonadditive: patients may have experienced more than 1 adverse event in each category. NSAID indicates nonsteroidal anti-inflammatory drug; ALT, alanine aminotransferase; and AST, aspartate aminotransferase.
†$P \leq .05$ vs celecoxib group.

For patients taking aspirin (Figure 2C), the annualized incidences of symptomatic ulcers and/or upper GI complications were not significantly different in patients taking celecoxib vs NSAIDs. For upper GI complications, the observed rates were 2.01% for patients taking celecoxib vs 2.12% for patients taking NSAIDs (6 events/298 patient-years vs 6 events/283 patient-years, respectively; $P=.92$). For upper GI ulcer complications plus symptomatic ulcers, the observed rates were 4.70% for patients taking celecoxib vs 6.00% for patients taking NSAIDs (14 events/298 patient-years vs 17 events/283 patient-years, respectively; $P=.49$). Including the 2 censored events (1 in each group), the rates were 2.35% and 2.47%, respectively, for upper GI ulcer complications and 5.03% and 6.36%, respectively, for upper GI ulcer complications plus symptomatic ulcers.

Other Adverse Effects

Adverse effects with an incidence of at least 5% in either treatment group during the 6-month treatment period were GI symptoms, upper respiratory tract infection or related symptoms, headache, and rash. Adverse effects causing withdrawal with an incidence of at least 1% in either treatment group were GI symptoms, rash, and elevated transaminase levels. For these categories, celecoxib was associated with equivalent or lower incidences of adverse effects and withdrawals compared with NSAID therapy, with the exceptions of rash and pruritus (TABLE 4).

Serious adverse effects (representing hospitalizations or malignancies detected during the 6-month treatment period) were reported for 4.3% of celecoxib patients (172 events/3987 patients) and 4.2% of NSAID patients (168 events/3981 patients). The most common serious adverse effects in patients taking celecoxib and NSAIDs were accidental fractures (7 and 8 events, respectively), back pain (8 and 8 events, respectively), pneumonia (9 and 9 events, respectively), cardiac failure (9 and 10 events, respectively), myocardial infarction (10 and 10 events, re-

spectively), and coronary artery disease (9 and 7 events, respectively). No serious rashes or unexpected serious adverse events were observed in patients taking celecoxib.

The overall incidence of GI symptoms experienced by patients taking celecoxib was significantly lower than by those taking NSAIDs, as was the rate of withdrawal due to GI intolerability (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common with celecoxib than with NSAIDs, although there was no difference in the incidence of diarrhea (Table 4).

The overall incidence of bleeding-related adverse events, and specifically, anemia and hematochezia, experienced by patients taking celecoxib was significantly lower than that among patients taking NSAIDs for all patients and for those not taking aspirin (Table 4). Similar results were noted for patients taking aspirin; the incidences of all bleeding-related adverse events were 4.0% and 8.3% for patients taking celecoxib and NSAIDs, respectively, and for anemia were 2.6% and 6.4%, respectively ($P<.001$ for both comparisons). Celecoxib was also associated with a lower incidence ($P<.001$) of clinically meaningful reductions in hematocrit and/or hemoglobin for the entire patient cohort than NSAIDs (FIGURE 3). A lower incidence was noted both in patients not taking aspirin (1.3% vs 3.4% in patients taking celecoxib and NSAIDs, respectively; $P<.001$) and patients taking aspirin (2.6% vs 4.9% in the 2 groups, respectively; $P=.02$). This difference persisted when all cases selected by the GI events committee for adjudication were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers, or other diagnosed GI disease (Figure 3). Mean serum iron–iron binding capacity ratios increased in patients taking celecoxib and decreased in patients taking NSAIDs (1.4% vs −2.3%; $P=.007$).

As shown in FIGURE 4, the incidence of serum ALT or AST elevations that exceeded 3 times the upper limit of normal was several-fold and statistically significantly higher in patients receiving NSAIDs than those receiving celecoxib. The incidence of ALT elevation for diclofenac was 3.2% vs 0.3% for ibuprofen; for AST, it was 1.8% vs 0.1%, respectively. Similarly, investigators reported a significantly higher incidence of adverse effects related to elevated ALT and AST with NSAID treatment (Table 4). Study withdrawals due to such elevations were also higher in patients receiving NSAIDs (Table 4). Overall, 97% of ALT and AST abnormalities occurred in patients receiving diclofenac.

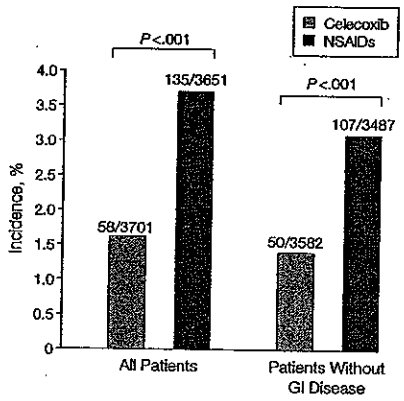
The overall incidence of renal adverse effects, and the incidence of increased creatinine and hypertension in particular, were significantly lower in patients receiving celecoxib than in those receiving NSAIDs (Table 4). Also, significantly more patients receiving NSAIDs exhibited clinically significant elevations in serum creatinine and/or serum urea nitrogen levels than with celecoxib (Figure 4).

The overall incidence of cardiovascular events, and the incidences of cerebrovascular events and myocardial infarction in particular, were similar in the 2 treatment groups (Table 4). No treatment-related differences in such events were apparent in the cohort of patients not taking aspirin for cardiovascular prophylaxis (Table 4). Incidence of myocardial infarction in patients taking either celecoxib or NSAIDs was 0.3%, with 95% CIs of 0.12% to 0.46% and 0.14% to 0.49%, respectively. For patients not taking aspirin, incidence of myocardial infarction in patients taking celecoxib was less than 0.10% (95% CI, 0.02%-0.28%) and was also 0.10% (95% CI, 0.03%-0.32%) in patients taking NSAIDs.

COMMENT

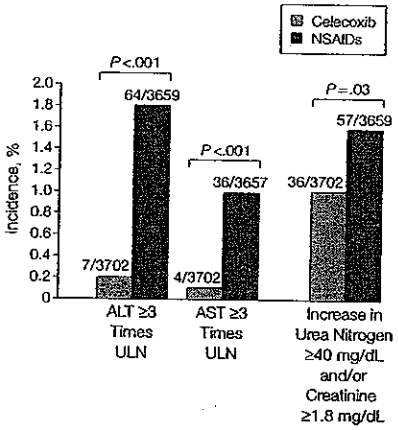
This study determined that celecoxib, a COX-2–specific inhibitor, when used for 6 months in a dosage 2 to 4 times the maximum therapeutic dosage, is associated with a lower incidence of combined clinical upper GI events than comparator NSAIDs (ibuprofen and di-

Figure 3. Patients With Decreases in Hematocrit and/or Hemoglobin at 6 Months



Data are shown for patients with decreases from pretreatment levels in hematocrit of 10 percentage points or more, in hemoglobin of 20 g/L or more, or both. Results for the entire study population are shown on the left. On the right, results for all patients excluding those with an upper gastrointestinal (GI) ulcer complication, symptomatic ulcer, or other diagnosed GI disease are shown. NSAIDs indicates nonsteroidal anti-inflammatory drugs. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.

Figure 4. Patients With Increases in Serum Creatinine and/or Serum Urea Nitrogen and With Elevations in ALT and AST at 6 Months



Data are shown for patients with increases from pretreatment levels in serum creatinine to 1.8 mg/dL (159 μmol/L) or more, in serum urea nitrogen to 40 mg/dL (14.3 mmol/L) or more, or both; and for patients with elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to a level of at least 3 times the upper limit of normal (ULN). In the nonsteroidal anti-inflammatory drug (NSAID) group, 97% of ALT and AST abnormalities occurred in patients taking diclofenac. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.

clofenac) used at standard therapeutic dosages.

In this study, patients taking NSAIDs had significantly higher rates of symptomatic ulcers or ulcer complications than did patients taking celecoxib, but the rate for ulcer complications did not differ. The statistically indistinguishable rate of ulcer complications associated with celecoxib and NSAIDs appears to be a function of the higher-than-expected event rate observed in the celecoxib group. The previously reported annualized incidence rate for ulcer complications in patients taking celecoxib (used for the sample size determination) was 0.2%, obtained from pooled analyses of 14 randomized controlled trials.[15]

This increased ulcer complication rate was likely attributable to higher-than-anticipated concurrent low-dosage aspirin use. The percentage of patients using low-dosage aspirin for cardiovascular prophylaxis was nearly double that seen in other clinical trials that we have conducted recently, albeit within the range reported for the general population.[24] Low-dosage aspirin therapy has clearly been associated with serious GI ulcer complications.[25-29]

In contrast, analysis of non–aspirin users alone demonstrated that celecoxib was associated with a significantly lower incidence of symptomatic ulcers and/or ulcer complications compared with NSAIDs. The rate of ulcer complications in non–aspirin users taking celecoxib (0.44%) is similar to the background rate of ulcer complications observed in patients not taking NSAIDs or aspirin in the general population (0.1%-0.4%).[8,9,11,12,30-33]

The observed incidences of symptomatic ulcers and/or ulcer complications were not significantly different in patients taking celecoxib vs NSAIDs who were also taking concomitant low-dosage aspirin. Data from endoscopic trials suggest that there may be a significant but smaller risk reduction in patients taking low-dosage aspirin, but this remains to be proven in terms of clinical outcomes.[34]

In addition to the assessment of GI effects, the present study determined that the increased dosage of celecoxib used in this study did not change the adverse effect profile observed at lower dosages.[20,21,35]

Of note, celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin and/or hematocrit compared with NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers, and other GI diseases were excluded. Celecoxib was also better tolerated than NSAIDs, as evidenced by the decreased incidence of GI symptoms and withdrawals for such symptoms.

The clinical consequences of NSAIDs on kidneys are heterogeneous, and, at present, the relative importance of COX-1 and COX-2 in the human kidney is not well defined.[36] Regardless, celecoxib appeared to be associated with significantly less renal toxicity compared with NSAID therapy in this study.

Although it has been hypothesized that COX-2–specific inhibitors might increase the risk of cardiovascular thromboembolic events via inhibition of vascular prostacyclin synthesis without a corresponding inhibition of platelet thromboxane, no such increase was evident in the current study.[37] In both the entire study population and the cohort not taking aspirin (who would conjecturally be at greatest risk of such an effect), the incidence of cardiovascular events, particularly myocardial infarction, was comparable between the celecoxib and NSAID groups.

Despite the size and duration of this trial, the populations of patients with OA and RA are much larger and therapy continues for substantially longer than 6 months.[38] Moreover, many patients with OA and RA have comorbid illnesses (eg, active GI disease) that would have excluded them from the current study. Consequently, the results of this study do not address the occurrence of rare adverse events, nor can they be extrapolated to all patients seen in general clinical practice.

Despite these caveats, however, our results demonstrate that celecoxib, at a dosage 2- to 4-fold greater than the maximum therapeutic dosages and those approved for labeling for RA and OA, is associated with a lower rate of upper GI toxic effects compared with standard therapeutic dosages of NSAIDs. This finding supports the COX-2 hypothesis that COX-2–specific agents exhibit decreased GI toxic effects.[17,39] Despite the high dosage used, other adverse effects did not emerge. Our findings thus have significant implications with respect to drug therapy for the symptomatic treatment of RA and OA.

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Financial Disclosures: Ms Burr and Drs Zhao, Kent, Lefkowith, Verburg, and Geis are employees of Pharmacia, manufacturer of celecoxib. In addition, all authors who are not Pharmacia employees are paid consultants for Pharmacia.

Funding/Support: This study was funded by Pharmacia.

Acknowledgment: We acknowledge the contributions of Dave Callison, Kirsten Katz, Beverly Paperiello, and June Kaiser, who monitored the study, and Clem Maurath, who provided statistical support.

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EXHIBIT 2

PR Newswire

April 17, 2000, Monday

SECTION: aDOMESTIC NEWS

DISTRIBUTION: TO MEDICAL EDITOR

LENGTH: 1504 words

HEADLINE: New Findings Presented on Celebrex(R) Safety and Tolerability From Long-Term Outcomes Study of 8,000 Arthritis Patients;

--Long-term safety studied in major organ systems, at 4 times the OA dose

--Ibuprofen and diclofenac found to cause significantly greater GI blood loss than Celebrex

DATELINE: CHICAGO, April 17

BODY:

In a landmark study to assess the overall long-term safety of the COX-2 specific inhibitor Celebrex(R) (celecoxib capsules), arthritis patients taking four times the recommended osteoarthritis (OA) dose of the drug experienced fewer symptomatic gastrointestinal (GI) ulcers and ulcer complications than patients taking ibuprofen and diclofenac -- a difference that was statistically significant based on a combined analysis of Celebrex versus these two traditional nonsteroidal anti-inflammatory drugs (NSAIDs). The findings, presented at the American College of Physicians annual meeting, also demonstrated differences on a variety of measures in renal and liver toxicity among those taking Celebrex or the NSAID comparators, two of the world's most widely prescribed drugs of this kind. Importantly, Celebrex showed no increase in thromboembolic or other cardiovascular-related events, even among non-aspirin users.

Also, in comparison to Celebrex, ibuprofen and diclofenac were associated

with a significantly greater GI blood loss -- equivalent to two pints or more -- over the course of the study, even in patients not experiencing bleeding ulcers. Such blood loss can often signal serious hidden damage throughout the GI tract.

Groundbreaking Study Reflects Real-World Practice

The Celecoxib Long-term Arthritis Safety Study, an approximately 13-month, multi-center, randomized, double-blind outcomes trial of about 8,000 arthritis patients -- 5,800 with OA and 2,200 with rheumatoid arthritis (RA) -- was designed to mirror everyday clinical practice by enrolling a broad spectrum of patients, including adult patients of all ages and disease severity, and patients taking low-dose aspirin for cardioprotection. The study, designed to obtain a rigorous assessment of Celebrex safety, compared four times the recommended OA dose of Celebrex (800 mg daily) to typical daily doses of ibuprofen (2400 mg daily) and diclofenac (150 mg daily). The Celebrex study dose is twice the highest recommended RA dose.

"No previous study has examined such a broad range of GI side effects -- which encompass events ranging from serious and often devastating GI ulcers and ulcer complications, to silent but medically important damage to the lining of the intestine, to symptoms like abdominal pain," said Lee S. Simon, M.D., associate professor of medicine, Harvard Medical School. "We've known the serious risks of traditional NSAIDs for some time, but these long-term findings show that patients taking Celebrex, in contrast to those on ibuprofen or diclofenac, experienced fewer treatment-related side effects in a number of important areas. These side effects often limit patients' ability to maintain their therapy and get the arthritis pain relief they require."

Researchers estimate that up to 30 percent of patients taking traditional NSAIDs develop persistent GI symptoms, and more than 10 percent of all patients

discontinue treatment.(1) An estimated 33 million people take traditional NSAIDs regularly. (2)

The study, funded by Searle and Pfizer Inc, found that Celebrex patients experienced significantly fewer symptomatic GI ulcers and ulcer complications compared with ibuprofen or diclofenac. Celebrex was also associated with numerically fewer ulcer complications than the NSAID comparators among all patients, and 64 percent fewer of these serious events among non-aspirin users -- a statistically significant difference. It is well known that aspirin is an independent risk factor for GI complications. Ulcer complications typically lead to hospitalization, and in some cases, death. Further, patients in the study reported Celebrex to be well tolerated, with dyspepsia, nausea and abdominal pain occurring at a significantly lower rate than with diclofenac.

"This rigorous outcomes trial set the bar higher than any previous study of its kind. It included a large number of patients who received four times the recommended OA dose of Celebrex for up to 13 months. It also compared Celebrex with commonly used traditional NSAIDs -- ibuprofen, one of the most well tolerated; and diclofenac, extensively used throughout the world," said Fred Silverstein, M.D., chairperson of the study's external review board. "Even at these very high doses, Celebrex showed sustained safety and tolerability in organ systems often affected by NSAIDs. As such, these are compelling findings for physicians to consider when treating arthritis patients."

Beyond GI Events: Safety Results in Major Organ Systems

In addition, the study examined the renal, liver and cardiovascular safety profile of Celebrex. Observed rates of various renal abnormalities and renal complications among Celebrex-treated patients were significantly lower as compared with diclofenac and ibuprofen, respectively. Moreover, in this study, significantly more patients developed hypertension or edema on ibuprofen, and

kidney or liver abnormalities on diclofenac, compared to the Celebrex group. Furthermore, Celebrex showed no increases in thromboembolic events (such as myocardial infarctions and stroke) or other cardiovascular adverse events compared with the traditional NSAID comparators. This is an important finding in light of the fact that about 40 percent of patients in each arm of the study had a history of cardiovascular disease, and about half of these patients were taking low-dose aspirin.

The incidence of skin rash was significantly higher with Celebrex -- at four times the recommended OA dose – compared with both of the traditional NSAIDs. No serious rashes were observed. Other adverse events most commonly reported with Celebrex in these studies, at approximately the same rate as the comparators, included colds and sinusitis.

Many of the estimated 43 million Americans(3) with OA and RA use NSAIDs, which can lead to stomach ulcers and other serious complications, and are the greatest source of serious adverse drug reactions reported to the U.S. Food and Drug Administration(4). These GI side effects often show no obvious signs or symptoms and go undiagnosed until patients are admitted to the hospital emergency room. Typically 60 to 80 percent of GI complications resulting from NSAIDs occur without previous symptoms.(5),(6)

Patients who have a known allergic reaction to celecoxib, certain sulfa drugs called sulfonamides, aspirin or NSAIDs should not use Celebrex. As with all NSAIDs, serious GI tract ulcerations can occur without warning symptoms. Physicians and patients should remain alert to the signs and symptoms of GI bleeding. Concomitant administration of aspirin with Celebrex may result in an increased risk of GI ulceration or other complications, compared to Celebrex alone. Celebrex does not affect platelet function and therefore should not be used for cardiovascular prophylaxis. As with all NSAIDs, Celebrex should be used

with caution in patients with fluid retention, hypertension, or heart failure. In studies, the most common side effects of Celebrex were dyspepsia, diarrhea and abdominal pain, which were generally mild to moderate.

Celebrex is co-promoted by Searle, now part of Pharmacia Corporation, and Pfizer Inc.

Pharmacia Corporation (NYSE: PHA) is a leading global pharmaceutical company created through the merger of Pharmacia & Upjohn with Monsanto Company and its G.D. Searle unit. Pharmacia has a broad product portfolio, a robust pipeline of new medicines, and an annual investment of more than $2 billion in pharmaceutical research and development.

Pfizer Inc (NYSE: PFE) is a research-based, global pharmaceutical company that discovers, develops, manufactures and markets innovative medicines for humans and animals. The company reported revenues of more than $16 billion in 1999 and expects to spend about $3.2 billion on research and development this year. For more information on Pfizer, access www.pfizer.com.

For complete prescribing information on Celebrex, access www.celebrex.com or call toll-free 888-735-3214.

(1) Singh G, Ramey DR, NSAID induced gastrointestinal complications: the ARAMIS perspective -- 1997. J Rheumatology, 25 (suppl 51), 1998, pp. 8-16.

(2) Roper Starch Worldwide NSAID Risk Survey, January 1998. [Statistic projected from survey: 33 million Americans use NSAIDs to relieve any kind of pain on at least two occasions within 12 months for at least five consecutive days.]

(3) National Arthritis Action Plan, AF, ASTHO, CDC, 1999.

(4) SRI International, February 1997.

(5) Armstrong and Blower. Gut. 1987;28:527-532.

(6) Singh et al. Archives of Internal Medicine. 1996; 156:1530-1536.

SOURCE Searle

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URL: http://www.prnewswire.com

EXHIBIT 3

PHARMACIA CORPORATION
Moderator: Hakan Astrom
April 25, 2000
10:00 a.m. EST

OPERATOR: Good morning ladies and gentlemen, and welcome to your Pharmacia Corporation First Quarter Earnings Release Conference Call.

At this time, all participants have been placed on a listen-only mode, and the floor will be open for questions and comments following the presentation. We ask you please use your handset while posing a question to ensure sound quality.

It is now my pleasure to now turn the floor over to your host, Senior Vice President of Corporate Strategy & Investor Relations, Mr. Hakan Astrom.

Sir, the floor is yours.

HAKAN ASTROM, SENIOR VICE PRESIDENT OF CORPORATE STRATEGY & INVESTOR RELATIONS, PHARMACIA CORPORATION: Thank you, Kathleen. Hello and welcome to our first quarterly conference call, and thank you for joining us today.

Before proceeding, council has asked me to refer you to the final page of the release for information regarding any forward-looking statements made during this call. Joining me this morning for the call at our Peapack corporate headquarters are Chief Executive Officer, Fred Hassan, Chris Coughlin our Chief Financial Officer, Carrie Cox, Head of Global Business Management, Al Heller, Head of our Searle Unit, and Hendrik Verfaillie, CEO of our Monsanto Agriculture Business.

Fred will begin with an overview of the quarter, followed by a financial perspective from Chris, and a review of our product performance by Al and Carrie. Hendrik will discuss the agriculture business, and then we will open up for Q&A. Fred.

FRED HASSAN, CHIEF EXECUTIVE OFFICER, PHARMACIA CORPORATION: Thank you, Hakan, and welcome everyone to our first quarterly earnings call for the new Pharmacia Corporation. We are pleased to be delivering good earnings growth news today. The 27% EPS increase is in line with our long-term growth plan. As you also see in our earnings release today, we have seen our combined global pharmaceutical business grow by 10% over the same period last year. Our Ag revenues were in line with our expectations and reflect the seasonal nature of the business. So, once more, we are pleased with the corporate performance, which is right in line with our expectations.

I would like to draw your attention to what we see as the two primary factors impacting our performance. The first is the exceptional strength of our product portfolio and the success we are seeing with those products in our key markets. The second is the efficiency and smoothness of our merger integration process.

In terms of the integration process, Pharmacia Corporation goes down in the record books as perhaps the fastest merger ever in the global pharmaceutical industry, and I am pleased to report today that integration continues ahead of schedule. In recent days, we have appointed the management committee, the group of top managers who will work closely with me to run the business from our headquarters here in Peapack. Our R&D organizations are well advanced in their knowledge sharing and integration planning, and our commercial business is also integrating worldwide. This very rapid and orderly integration process owed much to the experienced top management team that we have assembled, and in particular, to the strong track record of this team in making mergers work. That is why we have great confidence that we will succeed in the area where most mergers fail - the soft, human factors of management and business culture. Mergers are never easy, but we are seeing very encouraging evidence of teamwork and shared goals across the organization. We know that top line growth in our industry is critical to making mergers work and we are focused on top line growth through this merger process.

The other driver of our performance is, of course, our product performance, and Carrie and Al will discuss this in detail in just a moment. I would just like to underscore some key highlights. With Celebrex, we now have exciting new data that shows that Celebrex has a truly exceptional safety profile. This makes us feel good at a time when other products have been affected by safety concerns. Our biggest upside over the next 18 months will be the launch of Celebrex in Europe. We're taking an aggressive approach there and will be investing aggressively for long-term growth in Europe.

Regarding the claims by the University of Rochester regarding patent rights, I'd like you to be aware that I have personally reviewed the situation. I am very confident that our intellectual property situation is very solid, and after a thorough review of the patent and the legal framework, we remain very comfortable about the position of Celebrex.

Let me also draw your attention to our product flow. Pharmacia Corporation is truly unique in our industry in terms of the number and quality of new filings and approvals. In just the past week, you have heard of the FDA approval of our new antibiotic Zyvox, followed quickly by FDA approval of Camptosar for first-line treatment of colorectal cancer.

The approval of Zyvox with a positive label makes us a leader in the new era of antibiotics. We are very pleased to see that U.S. Regulatory Authorities and health care professionals share our conviction that Zyvox should not be reserved, but rather should be used early and appropriately to cure serious hospital infections. And, of course, these

developments are on top of the good performances we continue to see from our key existing products such as Detrol and Xalatan.

In summary, we are very satisfied with our progress so far and we have reason to expect our vigorous growth story to continue. This growth will be powered by top line expansion, but we will also be relentless in our actions to drive out costs from the system and deliver the synergies we promised. However, we will be managing cost reductions very carefully. We will be putting a priority on continuing the high performance of our products and also in assuring the success of new launches such as Zyvox and Celebrex, especially Celebrex, in Europe.

To give you further details on our financials, I will now turn the call over to Chris Coughlin. Chris.

CHRIS COUGHLIN, CHIEF FINANCIAL OFFICER, PHARMACIA CORPORATION: Thank you, Fred.

We are very pleased today to be reporting our combined earnings for the first quarter following the completion of our merger just three weeks ago on March 31st. The merger has been accounted for as a pooling of interest, so all prior periods have been restated. I hope that you have received our historical pro forma financial results for 1999 to assist you in evaluating our performance going forward. This information is also available on our corporate Web site.

Our combined earnings per share for the full-year last year 1999, was $1.11, and for the first quarter of last year was $0.26. These earnings reflect the impact of the Sugen and Sensus acquisitions. For comparison purposes, it does not include special charges such as restructuring or the earnings from the discontinued consumer and nutrition businesses of Monsanto.

I would also like to indicate that beginning with the second quarter earnings release, we will be providing more detailed financial breakdowns between our pharmaceutical and agricultural businesses, including income statement breakdowns.

Turning to our news release, we are pleased to be reporting a 10% increase in pharmaceutical sales driven by our key products in our major markets. Agricultural sales declined 2% in the first quarter. Foreign exchange had a 2% unfavorable impact on sales in the quarter due primarily to weaker European currencies.

As noted in our release, our gross margin improved by approximately one percentage point to more than 67% as a result of improved margins in the pharmaceutical business. Our selling, general and administrative expenses represented 35% of sales in the first quarter versus 33% of sales in 1999. This SG&A was slightly higher due to sales force expansion initiatives and higher promotional spending for new product launches, in particular, Celebrex. SG&A was reduced by a milestone payment received from Pfizer on Celebrex.

CHRIS COUGHLIN: Research and Development expenses decreased slightly in the quarter. Last year's first quarter R&D included costs associated with the closure of the Fibans cardiovascular program. In addition, our spending on agricultural R&D was reduced as a result of increased focus on the company's four key crops.

Other income amounted to approximately $59 million in the quarter impacted in part by a gain on the previously announced sale of the Pharmacia and Upjohn nutrition business in China. I will also note that the profit sharing payment made to our partner on Ambien is recorded on this line. That profit sharing payment increased to 40% from 18% last year.

The net result is a very strong 27% increase in earnings per share from our continuing business. As noted in the release, merger related costs totaled approximately $460 million in the quarter. This includes a non-cash charge of approximately $230 million for certain Monsanto stock options, which were repriced in conjunction with change of control provisions resulting from the merger. It also includes other one-time change of control costs as well as merger transaction costs.

You will note that we are not recording any restructuring costs this quarter. As you know, we have provided preliminary estimates of $500 to $800 million in restructuring costs that will be related to the merger and will be taken over the next two years. You will note in the release that during the quarter the company continued to make progress in its program to divest the Monsanto nutrition and consumer businesses. Proceeds of approximately $1.7 billion from the sale of these businesses that we announced during the quarter will be used to pay down debt and for other corporate purposes. This is right in line with the guidance we have previously provided. The net after tax gain on these sales reported in the quarter was $55 million.

You will also note that SG&A in the quarter includes $100 million in charitable donations made by Monsanto from the proceeds of the sale of the tabletop sweetener business. The donations include contributions to the Monsanto fund and to a patient assistance program known as "Patients in Need."

Looking ahead to the second quarter and the rest of the year, we remain committed to proceeding with a partial initial public offering of our agricultural unit. We expect to complete the IPO in late summer subject to regulatory approvals and appropriate market conditions. Let me add that due to the planned IPO of our agriculture business, we are not able to provide guidance on the future performance expectations of this business.

Regarding our total company earnings for the rest of the year, we expect second quarter EPS growth of 15 to 20%. The second quarter is weighted more towards the agricultural business due to its seasonal nature. In the third and fourth quarters, results will be more heavily influenced by the pharmaceutical business and will begin to reflect synergies from the merger.

In terms of earnings per share for the full year, the current consensus analyst estimate is $1.57 with most analysts at $1.55. We are comfortable with these estimates which represent a 40% increase over 1999, and are consistent with management guidance provided earlier this year.

Now, we will hear from Carrie regarding the performance of our pharmaceutical products. Carrie.

CARRIE COX, HEAD OF GLOBAL BUSINESS MANAGEMENT, PHARMACIA CORPORATION: Thank you, Chris, and good morning.

The 10% increase in pharmaceutical sales for the first quarter was driven primarily by the growth of our key prescription products including Celebrex, Xalatan, Detrol, and Camptosar. They all continued to demonstrate robust double-digit increases over the prior year. U.S. sales of Celebrex were $534 million, an increase of 92% over first quarter '99. Global sales of Xalatan increased 58%, Detrol sales grew 55%, while Camptosar increased 25% over the same period last year.

I will comment further in a few moments, but first let me ask Al Heller to take us through the performance of Celebrex.

AL HELLER, HEAD OF SEARLE UNITS, PHARMACIA CORPORATION: Thanks, Carrie.

Turning to Celebrex, as Fred mentioned, first cut data from our Celebrex long-term safety outcome study was presented at the American College of Physicians on April15th, and I will spend some time reviewing the highlights of that study. But first, I would like to briefly review first quarter results and the regulatory status of Celebrex.

Global Celebrex sales for the quarter were $534 million, with $484 million in U.S. In the U.S., Celebrex continues to enjoy a substantial advantage versus Vioxx in refill rates, capsules per prescription, and average days therapy per prescription meaning that every Celebrex new prescription leverages into substantially more sales for Pharmacia than Merck gets from a Vioxx new prescription. This is evidenced by the fact that Celebrex's first quarter U.S. sales were close to 60% higher than Vioxx's first quarter U.S. sales.

To date, Celebrex is currently approved in 46 countries and at the end of March, Celebrex successfully completed the 90-day review period for mutual recognition in the European Union. As Fred noted, we are placing a very high strategic priority on Europe for Celebrex and we will be working aggressively on launches across Europe throughout this year.

In addition to our European launches, another major growth driver will be the Celebrex long-term safety outcome study. The data presented to date is top line and first cut, but already a powerful story has emerged.

Let me take a few minutes now to cover the highlights of what was presented at the ACP meeting on the 15th. The top line take-away is that our landmark long-term arthritis study provides compelling evidence of the broad safety profile of Celebrex across a full spectrum of GI measures and in major organ systems versus the traditional NSAID comparators ibuprofen and diclofenac. The study was designed to mirror everyday clinical practice by enrolling a broad spectrum of patients including adult osteoarthritis and rheumatoid arthritis patients of all ages and disease severity and the patients taking low-dose aspirin for cardioprotection. We established an extremely high hurdle for Celebrex to demonstrate safety improvements against the traditional NSAIDs comparators by using four times the recommended OA dose of Celebrex versus typical daily doses of ibuprofen and diclofenac.

We chose our comparators deliberately. Ibuprofen is considered one of the most well tolerated and diclofenac is used widely throughout the world. We studied a wide range of GI side effects. The most serious such as ulcer complications which typically lead to hospitalization or death to symptomatic ulcers which lead to diagnostic and clinical intervention to treatment limiting GI symptoms such as dyspepsia and abdominal pain. We also studied the effects on major organs systems - renal, hepatic, and cardiovascular.

Let us first look at the GI findings, which I remind you compare Celebrex at four times the OA dose versus the standard prescription strength dose of traditional NSAIDs. Celebrex resulted in 42% fewer symptomatic ulcers and ulcer complications versus the NSAID comparators, a statistically significant difference. Among non-aspirin users, the difference was 53% in favor of Celebrex, also statistically significant.

When we focus only the most serious GI events, mainly ulcer complications which include perforations, gastric obstructions and GI bleeds, among all patients including those using low-dose aspirin, Celebrex resulted in 52% fewer ulcer complications, a finding that was just under statistical significance. Among non-aspirin users, the difference was 65%, which was statistically significant.

The study reinforced what has been known for some time – aspirin causes GI complications. When the impact of aspirin is removed, the data shows that the rate of ulcer complications among Celebrex patients is quite similar to the background rate found among people who do not use NSAIDs in the general population.

Celebrex was also found to be very well tolerated. The treatment limiting symptoms such as dyspepsia, nausea, and abdominal pain occurred at a significantly lower rate than with diclofenac. The study findings also showed Celebrex's safety in major organ systems versus the NSAID comparators. For example, Celebrex had a significantly lower incidence of edema and hypertension compared with ibuprofen and showed a significantly lower occurrence of kidney and liver function abnormalities compared with diclofenac. With Celebrex, physicians don't need to make

trade-offs on renal and hepatic safety, as they often must in choosing their traditional NSAIDs in order to treat the pain of arthritis.

The study also had some unexpected findings. We were surprised to find that compared to Celebrex, significantly more patients on the traditional NSAID comparators had noteworthy blood loss equivalent to two pints or more regardless of whether they experienced bleeding ulcers. These findings speak of the serious hindrance of these products throughout the entire GI tract.

Finally, even at these very high doses, Celebrex showed no increases in thromboembolic events such as stroke or heart attack, or other cardiovascular related events even among non-aspirin users. This is an important finding in light of the fact that 40% of the patients studied had a history of cardiovascular disease. In a recent news release and letter to investigators, Merck had suggested that any negative thromboembolic effect is associated with the therapeutic class as a whole.

It is interesting to note that Vioxx had these negative findings at two times their osteoarthritis dose whereas Celebrex showed no such findings even at four times our osteoarthritis dose, suggesting that any such effect might be molecule specific. Contrary to what you may have heard from Merck, the Celebrex data showed that there is no class related disadvantage in this important safety parameter.

To summarize, the long-term outcome data paints a clear and compelling picture of Celebrex's safety versus NSAIDs. Celebrex shows the comparable cardiovascular profile to NSAIDs and a superior profile in respect to ulcer complications, symptomatic ulcers, GI tolerability, blood loss, and renal and hepatic complications. We achieved these findings in a study that, as closely as possible, mirrored real world clinical practice, and we are confident that as physicians and managed care organizations gain awareness and understanding of these data that an even greater number of patients will benefit from the safety and efficacy of Celebrex. We look forward to presenting a fully analyzed data set from this trial to the FDA before mid-year.

Finally, let me comment on Ambien. In it's seventh year on the market, Ambien continues to show remarkable growth tenacity. First quarter sales represented a 15% increase over the prior year and this performance continues despite the significant competitive activities of Sonata, which launched last fall.

I will now turn it back over to Carrie.

CARRIE COX: Thank you, Al.

Xalatan turned in another outstanding performance in the quarter with global sales of $161 million representing a 58% increase over the same quarter a year ago. Sales of Xalatan in the U.S. were $86 million representing a 36%

increase over last year.

In the quarter, Xalatan new Rx volume grew significantly faster than the market resulting in a gain of nearly two share points. Sales in Europe accounted for 27% of global quarterly sales of the product and reflect an increase of 41% over first quarter '99. In fact, Xalatan continues to be the number one branded glaucoma product in all key European markets and is emerging as the new gold standard in glaucoma therapy worldwide.

In Japan, the second leading glaucoma market in the world, we are particularly proud that in only nine months Xalatan has captured an impressive 22% market share in March. Xalatan is now firmly the number two product in the Japanese glaucoma market and continues to be one of the most successful product launches ever in Japan.

As you know, we submitted an NDA for our new Xalatan combo product, Xalcom, in the U.S. in fourth quarter 1999, and in Europe in first quarter 2000. Since we were granted priority review in the U.S., we are anticipating a launch of this exciting new product by the end of this year.

Global sales of Detrol in the first quarter reached $100 million, up 55% over first quarter '99, with strong performance in U.S. and in Europe. U.S. sales grew by 51% with quarterly sales of $76 million. In Europe, Detrusitol grew 64% over the prior year to reach first quarter sales of $22 million.

In the U.S., we continue a strong leadership position in this market with 45% new Rx market share and 46% in TRxs for the first quarter. From January to March, Detrol's new Rx volume growth outpaced the market. Our new Rx volume increased by over 21% compared to the overall market growth of 18%. Detrol TRx volumes during the same period increased by 14% compared to the overall market volume growth of 13%.

In March, 466 Searle sales reps began selling Detrol, now giving us 1,800 sales representatives selling Detrol in the U.S. Each and every one of these sales representatives since March has been armed with new clinical data that clearly demonstrates the efficacy of Detrol on incontinence episodes. We believe this gives us the firepower to contain Ditropan XL, while increasing our market share. Although it is still very early, those of you who follow weekly prescriptions know that over the last five weeks of new Rx, Detrol has gained over a point in market share.

As I have emphasized before, though, the over active bladder market remains very underdeveloped. Estimates indicate that only 5 to 10% of patients are being treated for OAB. Primary care physicians are key to initiating treatment for the vast majority of patients. In January 2000, primary care physicians were responsible for about 60% of the Detrol total prescriptions, up 15% from the year before. This is a result of our strategy to grow our market share while growing the market for OAB.

As you know, we have filed U.S. and EU applications for the once daily formulation of Detrol and expect FDA action by year-end. Data on Detrol XL will be presented to physicians for the first time next month during the annual AUA meeting.

Sales of Camptosar for the quarter reached $80 million, an increase of 25% over first quarter '99. And as was mentioned just last week, we received FDA approval for the use of Camptosar in first-line treatment of colorectal cancer. This it the first new product approved for first-line treatment of colorectal cancer in 40 years, and the FDA Advisory Committee suggested that the regimen containing Camptosar and 5-FU/LV should be the new standard against which future therapies are compared.

Adding Camptosar adds survival benefits and delays the progression of the disease, yet also has a manageable side effect profile. The number of patients who are eligible for first-line use is about twice that for second and third stage use.

Turning to Zyvox, the FDA approved Zyvox on April 18th. We are very pleased with the strength of the label. With five indications for a broad range of Gram-positive bacteria, including those sensitive to and resistant to other antibiotics. Zyvox is also currently being reviewed by the UK medicines control agency and we are hoping to receive clearance by year-end. We'll then file through the mutual recognition process to receive approval across Europe. A filing in Japan is anticipated for later this year.

Zyvox is the first agent in the first new class of antibiotics in 35 years. We have priced Zyvox daily IV therapy in the U.S. at $115 per day, less than half the price of Synercid's daily therapy cost, while Zyvox oral daily therapy cost is $85 per day. Because of its excellent efficacy and tolerability profile, we plan to position Zyvox for empiric use in the hospital setting in known or suspected Gram-positive infections. We do not believe that it is in the best interests or patients or payers to restrict Zyvox use. In fact due to its unique mode of action, early use of Zyvox can help to reduce the growing problem of antibiotic resistant organisms. Zyvox attacks that purely in an entirely new way and stops protein production at the beginning of the process and at a point earlier than for any currently available antibiotic. It has fully bio available IV and oral formulations so no dosage adjustment is required to switch to the oral tablet or suspension. Zyvox is generally very well tolerated and its safety and convenience will enable patients to complete therapy and may lead to reduced length of hospital stay.

I'll now turn the call over to Hendrik for some comments on the agricultural business.

HENDRIK VERFAILLIE, CEO, MONSANTO AGRICULTURAL BUSINESS: Good morning, I'm pleased to discuss the first quarter results for Monsanto's agriculture business. Our agricultural business is built on integrated platform of seeds, crop protection products and gene-based technologies that offer farmers great choice and value. Our growth comes from our base businesses such as Roundup herbicide and conventional seeds, and from our new

products based on biotechnology and genomics, such as the Roundup Ready soybeans and corn, Bollgard insect-protected cotton, and Posilac for increased milk production in dairy. Despite difficult industry conditions, our Ag business is performing as expected.

I'd like to start this morning by discussing the broad conditions all companies in the agriculture industry face this year. First, low commodity prices especially on major row crops like corn and wheat and soybeans have depressed profits for farmers worldwide. As a result, growers are looking for every opportunity to reduce costs. Second, tough credit conditions in areas like Latin America have further compounded gross cash flow problems and reduced or delayed their purchase of crop protection products. Third, drought conditions persist in much of North America, following a warm, dry winter resulting in limited weed growth and thus reduced or delayed demand for herbicides. As a result, growers are faced with difficult decisions about the types of crops they'll plant and the crop protection products that they'll use. Many are delaying purchases or are choosing to farm without products that they would normally use.

Again, in light of these industry conditions, our Ag business performed as expected in the first quarter with net sales down 2%. Revenues for Roundup decreased by 5% as volume gains of 12% were offset by a combination of lower prices and a less favorable product mix. Volume gains year-to-date in United States and Europe were in excess of 20%. However, volumes in Canada and Latin America and in parts of Asia were down. In the United States volumes were particularly strong in the south where the warmer weather has allowed growers to prepare their fields earlier using a treatment of Roundup. In Latin America the first quarter is traditionally weak, as the key growing season in the Southern Hemisphere is in the second half of the year. Drought conditions in the fourth quarter of 1999, or the first quarter of 2000, also depressed volume sales.

Over the last year we have entered into several licensing arrangements with other crop protection companies, where we supply them glyphosate, the active ingredient of Roundup. Sales under these agreements grew substantially year-to-year; however, at this point, these competitive glyphosate products have not significantly affected sales of our branded Roundup herbicide.

Net sales from all seeds and biotechnology traits decreased by 1% compared with sales in the first quarter of last year. Sales of cotton traits were very strong, driven by increased demand particularly for seeds stacked with the combination of Roundup Ready and Bollgard traits. Offsetting that strength were lower corn and soybean seed and trait sales. Through the end of the first quarter, sales of seeds with biotech traits have been running consistent without prior expectations that overall acres of biotech crops will be flat or slightly up this season in the U.S. I would caution, however, that these initial sales reports don't reflect actual acres being planted by growers. Growers have the right to change their seed orders right up until the time until they plant. And as a result, the actual acreage planted is not final until the end of the second quarter.

Revenues for Roundup lawn and garden grew by 30%t year-to-year. Roundup lawn and garden is sold to consumer outlets like Wal Mart and Sam's. We continue to realize the cost benefits in the first quarter from the seed company integration program that we started last year and we expect to see continued cost improvement over the rest of the year as we reduce overhead and fully implement our restructuring programs.

Finally, as many of you know, the acceptance of agriculture biotechnology products is an issue Monsanto and the industry has faced during the last couple of years. This quarter, the biotech industry coalition launched it's U.S. information program. While it's too early for statistical feedback, the program appears to be going well. We have had good news from several government and research agencies on biotech this quarter, such as the National Academy of Sciences report issued in April, which confirmed the safety of food grown from genetically improved seeds. We believe that we now have the right efforts in place to continue to gain the freedom to operate worldwide. Biotechnology offers so many benefits that we are very confident that it will eventually succeed.

In summary considering the economic conditions, first quarter results were as we expected. We are confident in the strength of our integrated business platforms of Roundup, seeds and biotech traits and are focused on delivering our growth and cost targets.

Now I will turn the call over to Hakan for Q&A.

HAKAM ASTROM: Thank you, Hendrik. Operator we are now ready for questions.

OPERATOR: Thank you, sir, the floor is now open for questions. Our first question is coming from Steve Tighe of Merrill Lynch.

STEVE TIGHE, MERRILL LYNCH: Good morning. I was just wondering if you could talk about pharmaceutical sales growth of 10% in the context of what you indicated that you could do in terms of sales growth over the next three years. What factors will drive the increase in sales growth to the levels that you've set in terms of expectations?

FRED HASSAN: Steve, we continue to feel very confident about the three-year outlook. As you may remember, we had mentioned that there are five engines of growth that will add $4.5 billion in sales over the next three years. These five engines being Celebrex, Xalatan, Detrol, Campostar, and Zyvox. I'm very pleased to say that what we said earlier this year is still very much on track because the approvals for some of these products have occurred since that time. We are also very pleased with the CLASS data which has now come out for Celebrex and the European approval of Celebrex. So, everything we said earlier this year in terms of the growth outlook is very much intact and we feel very confident about $4.5 billion in new sales coming from these five products.

OPERATOR: The next question is coming from Barbara Ryan of BT Alex Brown.

BARBARA RYAN, BT ALEX BROWN: Good morning. As a follow up on the same theme, it looks like Celebrex in the U.S. has slowed from a sequential growth rate in the fourth quarter of 25% to about 6.5%, and the recent new prescription data continues to show you loosing share to Vioxx. It also appears that the VIGOR trial is going to show statistical significance in both PUBS, and POBS. There are a whole host of other products in the quarter that were either flat or down relative to the fourth quarter and they were notable among your list, and the gross margins were up about 100 basis points with year-on-year growth of Celebrex. I'm just wondering, what are going to be the drivers specifically of Celebrex in the U.S.? And what should we be looking for in gross margin improvements as these products year-on-year slow?

FRED HASSAN: I'll try to answer this question but I'll also ask Al to help me since he's much closer to the Celebrex situation. We believe that the COX-2 market could be very large and that the attractive part of the market is that there are two major players in this market – us and Merck. If you look at the new Rx shares of older products in the market, it's amazing that old products such as ibuprofen or naproxen have very large market shares in spite of these COX-2 agents being on the market. As a result of the new data that is coming out from Searle, as well as from Merck, we believe that the market is poised for major expansion over the next three or four years. And it'll become very difficult for managed care to prevent access to these products, especially when you look at figures like two pints of blood loss with the older NSAIDs. It is hard for managed care to hold back these products, and we think that it's going to grow. It's true that the quarterly numbers may not look that impressive, but if we look at the longer term, I think the outlook is very exciting. We do recognize that Merck is a strong competitor, but we are very encouraged by the prospect of market expansion. Al.

AL HELLER: The only thing I might add is that you have to recognize that something like 65% of the marketplace is still in the traditional NSAIDs. I think the strength of the data that we're showing, particularly with our outcome study, really speaks not only of the known dangers of the traditional NSAIDs but also points out some new and unexpected dangers such as the blood loss. That's really going to be a powerful tool for us to penetrate that 65% of the business. I share Fred's confidence that some of the flatness in the prescription growth rate you saw in the first quarter will definitely be accelerating going forward.

BARBARA RYAN: Related to the timing of potential label changes based on the two large trials, what realistically is the timetable we should be looking at for that change?

AL HELLER: I obviously cant' speak to the Vioxx label change if they will get one at all, but our expectations is to have our sNDA filed before the end of the second quarter. And I think that the data is significantly compelling to request from the FDA that they look at it on an expedited basis.

HAKAN ASTROM: You had a question on the gross margins.

BARBARA RYAN: Yes, thank you.

CHRIS COUGHLIN: In looking at the gross margin, I think that you'll be able to track this in more detail going forward as we provide you more detailed information in the future between our pharmaceutical and our agricultural businesses. We did see expanding gross margins in our pharmaceutical business that was partially offset by a decline in our gross margin as was expected in our Ag business as the pricing of Roundup has come down and we had that first quarter mix issue with Roundup. I think gross margins are continuing to expand in our pharmaceutical business and will continue throughout this year.

FRED HASSAN: I think you may want to note that Zyvox is a big new factor in our future and the product mix will be upgraded by this new product. Chris, I understand that the gross margin for Zyvox is above the average gross margin of the basket.

CHRIS COUGHLIN: Yes, it is.

HAKAN ASTROM: Thank you, I think we'll take the next question.

OPERATOR: Thank you the next question is coming from Ted Semegran of Brown Brothers.

TED SEMEGRAN, BROWN BROTHERS: Good morning. On the Ag side, it's hard to understand why Roundup sales were down when volumes were up globally 12%. Weren't the prices expected to only be down about 10% or less? The second issue relates to the Roundup Ready traits. Your early feel on the soybean market was that it might be up and the stacked traits cotton market looks like it's up at least a million or two acres, is that correct?

HENDRIK VERFAILLIE: First of all, in the Roundup prices, if you exclude the volume that was sold under these arrangements that we have of selling glyphosate to other companies, then the price decrease was in line with the past years – just below 10%. It is significant volume of glyphosate raw materials sold to other companies that drove down the price to a large extent. On the Roundup Ready traits, based on the intention surveys and based on actual sales of seed we are expecting that the acreage is going to be up in cotton, up slightly in soybeans and is going to be down slightly in corn. Overall, we still expect that the total biotech acres in the U.S. will be up slightly.

TED SEMEGRAN: Are you making reasonably good profits on the glyphosate sold to the third parties so that this lower price that you are talking about is not that significant an item?

HENDRIK VERFAILLIE: Yes, we still make significant profits on the product that we are selling to third parties, but obviously not as much as we would make from our branded Roundup products.

TED SEMEGRAN: Is the percent of glyphosate that is sold to third parties now 10% of the Roundup sales?

HENDRIK VERFAILLIE: I can't' give you any indication of that, but we would expect that over time that this is going to be around 10%.

HAKAN ASTROM: OK, thank you, we'll take the next question, please.

OPERATOR: Thank you, the next question is coming from Alan Sebulsky of Lincoln Capital.

ALAN SEBULSKY, LINCOLN CAPITAL: Could you just highlight whether there were any price increases in the quarter and whether there was any pipeline or de-stocking in major products?

CARRIE COX: We took price increases in the quarter on Xalatan and Detrol. There was some additional Y2K buildup on Camptasor at the end of the year last year that was worked down over the course of the quarter.

AL HELLER: Alan as far as the Searle products are concerned we took no price increase on the Searle products and there was some de-stocking around Celebrex and Ambien, so I think that a better growth comparative from a trade perspective for those products will be second quarter versus first quarter.

HAKAN ASTROM: Next question, please.

OPERATOR: Thank you the next question is coming from Ian Sanderson of SG Cowen.

IAN SANDERSON, SG COWEN: Yes, I have a couple of questions on the Ag business. You went through some of the backdrop issues on that business in Q1. Is there any sense that those issues are changing in Q2 from a market environment perspective, and is it possible that if you don't put up decent Q2 results on the Ag business that you may delay the IPO there?

HENDRIK VERFAILLIE: Obviously it is difficult to predict what the weather will do. The markets conditions that we have seen with low commodity prices and a shortage of credit in markets like Brazil and Eastern Europe will certainly continue for the foreseeable future, although I must say that we are starting to see some improvement in Asia and also in Latin America. If the trend that we have seen in the last few months on commodity prices were to continue, then I would expect that the economic conditions are going to be continuing for the future.

As Chris indicated, I really can't make any forecasts on the Ag results for the rest of the year, but the one thing I can say is that based on what we have experienced and delivered for the past 8 years, we have consistently grown the

Roundup business by 20%. It doesn't mean that we grew it by 20% every quarter. As a matter of fact, last year was an example where we grew by less than 20% in the first quarter but still accomplished a 20% growth rate by end of the year. Our business is seasonal and has up and down quarters based on weather conditions and based on when farmers plant and buy their products. If I look at what has happened in the past and in the first quarter, I am confident that we are on track.

IAN SANDERSON: Because the pricing environment may be slightly different, do you see units overtaking pricing declines for Roundup through the balance of the year?

HENDRIK VERFAILLIE: So far what we have seen is that the price in the market is about where we have expected it. As I said, the decline that we have seen in the market is in line with the historic price trends. For the traits we are charging the same price this year as we did last year, so we don't have any discounting going on in the biotech trades.

CHRIS COUGHLIN: Regarding the IPO timing, we are proceeding aggressively with our plans looking at late summer.

HAKAN ASTROM: Next question, please.

OPERATOR: Thank you the next question is coming from Christina Heuer, of Salomon Smith Barney.

CHRISTINA HEUER, SALOMON SMITH BARNEY: Thank you. My question is about Zyvox. One of the big concerns investors have had is whether or not this drug is going to be reserved. Carrie, you indicated that you certainly don't think that will be the case, but I'm wondering if you could point to anything in particular on the label or in your early experience with hospital formularies and managed care formularies to give us something a little bit more concrete to hang onto?

CARRIE COX: Probably the most significant thing is that while there were discussions through the regulatory process as to whether or not there should be any restrictions put on the drug, the firm conclusion to that was that it is not appropriate to restrict. I think that this is a good example of where the science is slightly more complicated than the superficial look, and you need to understand that one of the drivers of antibiotic resistance and the growth of the resistant organisms is in fact inappropriate use of antibiotics. The science definitely would suggest that the right way to use this product is empirically in serious infections. One of the specifics I can give you to support that is that even though the product has only been available now for a matter of hours we are already finding a great number of hospital orders coming directly to us bypassing the wholesalers. There's a great interest in getting immediate access to the product. As far as managed care goes, it's not really an issue here because our goal is to have use in the

hospital setting primarily. We don't believe it's appropriate to have this used as a community-based product. It's a hospital market not really managed care, per se.

HAKAN ASTROM: Thank you, we'll take three more questions.

OPERATOR: Thank you, sir, the next question comes from Richard Beleson of Capital Research.

RICHARD BELESON, CAPITAL RESEARCH: The question I have relates to Celebrex in the CLASS study. You had a statistically significant result in the non-aspirin users but non-significant result in the total population. Was that non-aspirin user population a predefined population or will the FDA be concerned that this is a retrospective analysis?

STEVE GEIST: Sure, the study was designed to mirror normal medical practice. In the protocol design we had identified that we were going to do analyses looking for risk factors for complications, such as aspirin use. So, we allowed aspirin users and non-aspirin users into the trial to mimic normal medical practice and we accounted in the protocol for doing the analysis of aspirin use. Al pointed out in the total patient population there was a two-fold reduction in complications and it was just shy of statistical significance, but when you pulled the aspirin users out it was a three-fold reduction, which was clearly statistically significant.

RICHARD BELESON: But is the FDA going to look at that and agree that it was a pre-defined patient case population with statistically significant results or will they say it is a retrospective analysis?

STEVE GEIST: I can't speculate on how the FDA will interpret data or assess the appropriateness of the data; however, we did design the study in conjunction with the FDA. We do think that the results do mirror medical practice and clearly demonstrate the GI safety profile of Celebrex in the general population, and, again, at four times the full OA dose.

RICHARD BELESON: Secondly, there was some discussion about whether or not the thromboembolic events are a molecule specific effect. What molecular mechanism or differentiating factors regarding Vioxx versus Celebrex might account for its causing thromboembolic events as opposed to being a class effect?

STEVE GEIST: We do know that it is not a class effect because we have not seen any evidence of thromboembolic events higher than that was seen with NSAIDs with Celebrex. We just know what's reported in the public domain about Vioxx and have the same information that you have which says that they did see a higher incidence, which was statistically higher than the naproxen. Now (regarding) the precise mechanism of that, we don't have that answer right now. We do know that Vioxx produces a dose-related increase in blood pressure and it has been

reported in the literature that with increases blood pressure there is an increased likelihood of stroke. The precise mechanism we can't determine as yet.

RICHARD BELESON: Is naproxen more effective in preventing thromboembolic events than diclofenac or ibuprofen?

STEVE GEIST: There is no evidence to support that conjecture.

HAKAN ASTROM: Thank you, can we have the next question please.

OPERATOR: Thank you, sir, the next question is coming from James Kelly of Credit Suisse First Boston.

JAMES KELLY, CREDIT SUISSE FIRST BOSTON: Good morning, could you just refresh us on the schedule of the flow of the JV payments on Ambien. I know you said it was 40% at this point; how does it go out over the next couple of years? Also, could you give us any data on the size of the milestone from Pfizer that you had in there? Thank you.

AL HELLER: The milestone payment from Pfizer was $70 million, and the scheduled payments is 60%/40% this year. It goes to 51%/49% next year and it continues that way through the remainder of the agreement which is April 15th of 2002.

HAKAN ASTROM: Now we'll take the final question please.

OPERATOR: Thank you. The final question is coming from Sturgis Woodberry of Oppenhiemer.

STURGIS WOODBERRY, OPPENHEIMER: Could you just outline your capital spending goals for this year and working capital investment goals?

CHRIS COUGHLIN: Since we just closed three weeks ago, we're in the process of putting together a new forecast for our capital spending and working capital. Right now we're running at about a 10% increase over last years first quarter in terms of capital, but we are doing a total re-evaluation as we look at the full integration plans between the two companies, so it's a little bit early right now. I think the current estimates of the two companies as independent companies was between $1.6 and $1.7 billion on capital and certainly I think it would be somewhat less than that, but we haven't established a final target as of yet.

HAKAN ASTROM: We are finished with the questions and Fred will have a concluding remark.

FRED HASSAN: Well, we are about three weeks into the merger and we feel very good about the merger process. We continue to believe that this merger makes a lot of sense and also the way we're managing the company going forward with a separate business approach is going to unlock a lot of value in both the pharma and the Ag businesses. In pharmaceuticals we are very encouraged by the sales outlook as we see the new product registrations occur and we're very confident that we'll also get that operating margin upgrade that we are looking for over the next three or four years. In Ag, we continue to be very excited about the prospects of biotechnology, which look a lot better now that they looked six months ago, and we also believe that the base business is very strong. We do recognize that on a quarter-to-quarter basis there's more volatility in the Ag business and we knew that going into this venture. We feel very good about this merger, and we very confident that when we speak to you again after the second quarter and the third quarter results are published that you will continue to hear good news. Thank you, once again.

HAKAN ASTROM: Thank you and operator we will now close the call, thank you.

OPERATOR: Thank you, ladies and gentlemen, this concludes today's teleconference. You may disconnect your line at this time.

EXHIBIT 4

Dow Jones News Service

April 17, 2000 Monday 12:12 PM GMT

LENGTH: 239 words

HEADLINE: Pfizer/Pharmacia Arthritis Product Effective In Study

BODY:

CHICAGO -(Dow Jones)- An 8,000-patient safety study of Pharmacia Corp.'s (PHA) and Pfizer Inc.'s (PFE) Celebrex arthritis drug found the product produced fewer gastrointestinal ulcers and other side effects than ibuprofen and diclofenac.

In a press release Monday, Pharmacia said participating patients took four times the recommended osteoarthritis dose of Celebrex, while a comparison group took ibuprofen and diclofenac, two traditional nonsteroidal anti-inflammatory drugs.

Both companies funded the study, which took place over 13 months and involved both osteoarthritis and rheumatoid arthritis patients.

Pharmacia said the study showed ibuprofen and diclofenac were associated with significantly greater gastrointestinal blood loss, even in patients not experiencing bleeding ulcers.

Patients reported that Celebrex was well tolerated, with nausea and abdominal pain occurring at a lower rate than with diclofenac.

The most common side effects with Celebrex were dyspepsia, diarrhea and abdominal pain.

In addition, Pharmacia said significantly more patients developed hypertension or edema on ibuprofen and more kidney or liver abnormalities on diclofenac, compared to Celebrex.

Celebrex showed no increase in thromboembolic events such as stroke or other cardiovascular-related events.

Pharmacia said the incidence of skin rash was significantly higher with Celebrex than with the NSAIDs.

-Emily Park; Dow Jones Newswires; 201-938-5400

NOTES:
PUBLISHER: Dow Jones & Company

LOAD-DATE: December 14, 2004

EXHIBIT 5

April 17, 2000 Monday 7:51 PM GMT

LENGTH: 504 words

HEADLINE: Pharmacia-Pfizer Study Underscores Celebrex Safety

BYLINE: By Beth M. Mantz

BODY:

NEW YORK -(Dow Jones)- Even at four times the dosage amount; Celebrex was found to be safer than the standard of care, according to a study by the drug's makers, Pharmacia Corp.'s (PHA) Searle unit and Pfizer Inc. (PFE).

The results underscore the point the two companies were attempting to prove: blockbuster Celebrex, a cox-2 inhibitor for treating osteoarthritis and rheumatoid arthritis, is safe, Jim Lefkowith, senior director of clinical research at Searle, told Dow Jones Newswires.

Although the 8,000-patient, 13-month safety study wasn't designed to test new indications or new patient populations, the long-term safety data bolster the drug's potential to generate additional sales.

For 1999, Celebrex sales were more than $1.5 billion. Launched at the end of January 1999, Celebrex had 16.6 million total prescriptions in 1999, including 9.7 million new ones and 6.9 million refills.

The study results indicated that even with an increased dosage to four times the recommended osteoarthritis dose and two times the rheumatoid arthritis dose, Celebrex produced fewer gastrointestinal ulcers and other side effects than the traditional nonsteroidal anti-inflammatory drugs - ibuprofen and diclofenac - considered the gold-standard treatment for both osteoarthritis and rheumatoid arthritis patients.

Additionally, significantly more trial patients developed hypertension or edema on ibuprofen, and more kidney or liver abnormalities on diclofenac, compared to Celebrex. The study also showed Celebrex didn't bring about an increase in thromboembolic events such as stroke or other cardiovascular-related events.

This study reveals data that impacts "the real world, showing a broad range of patients, taking a full range of medication for other diseases," said Lefkowith. It gives the "prescribing physicians reassurance and clinical trial support" of safety in recommending patients use Celebrex for their ailments.

Designed to provide additional safety details to the Food and Drug Administration for labeling changes, this study began before Celebrex was approved. Pharmacia intends to submit these trial results, but "whether the FDA changes the label is (the agency's) prerogative," he added.

Pharmacia continues to research and conduct clinical trials for extended indications of Celebrex, but Lefkowith wouldn't discuss ongoing trials.

But he did say the companies are interested in Celebrex and colorectal cancer. In December, Celebrex received FDA approval as an adjunctive treatment for familial adnomatous polyposis, a hereditary disease that often leads to colorectal cancer, and in March the two companies announced a new mutli-center study to test Celebrex in preventing the occurrence of adenomatous polyps, which potentially put people at an increased risk of colorectal cancer.

Additionally, Lefkowith is conducting an open-label safety trial that could corroborate the safety data, but the study doesn't examine traditional nonsteroidal anti-inflammatory drugs.

-Beth M. Mantz; Dow Jones Newswires; 201-938-5287

NOTES:
PUBLISHER: Dow Jones & Company

LOAD-DATE: December 14, 2004

EXHIBIT 6

April 17, 2000

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Pharmaceutical Industry

CELEBREX CLASS TRIAL CONFIRMS G.I. SAFETY (WITH A SLIGHT WRINKLE) – NO CARDIOVASCULAR RISK

Company	Ticker	Rating	Price (4/14/00)	52-Wk Range	Earnings Per Share 1999	Earnings Per Share 2000E	Earnings Per Share 2001E	Price/Earnings 2000E	Price/Earnings 2001E	Div. Yld.	Mkt. Cap. ($B)
Merck & Co.	MRK	MP	$63.81	$87-52	$2.45	$2.80	$3.00	22.8	21.3	1.9%	141.6
Pfizer	PFE	B	$37.94	$50-30	$0.87	$1.04	$1.22	36.5	31.1	1.0%	134.5
Pharmacia	PHA	B	$53.13	$66-43	$1.07	$1.55	$1.92	34.3	27.7	1.8%	29.6

Source: J.P. Morgan Securities Inc. estimates.
JPMS ratings: B = Buy; LTB = Long-Term Buy; MP = Market Performer; MU = Market Underperformer.

HIGHLIGHTS

- In a bit of a surprise, results of the Celebrex (Pharmacia) CLASS trial (on GI events vs. NSAIDs) were presented Sat. night (April 15).
- On a variety of measures, Celebrex showed clear statistical superiority on GI safety versus NSAIDs; however, the primary endpoint was a particularly high hurdle, and on this metric Celebrex narrowly missed statistical separation from NSAIDs.
- This appears to be due to the allowance of background aspirin therapy (for cardiovascular risk reduction) – which poses significant GI risk in its own right and may have clouded the GI difference between Celebrex and NSAIDs. Excluding the aspirin patients (22% of total), there was clear statistical GI-safety superiority for Celebrex.
- Celebrex showed no statistical difference from NSAIDs on any of a variety of cardiovascular risk factors. This contrasts to Merck's Vioxx in the VIGOR study, which did show that Vioxx patients experienced more thromboembolic events (i.e. stroke, heart attack) than NSAID patients. This may have been due to the anti-clotting benefits of NSAIDs and the fact that VIGOR did not allow background aspirin therapy. However, in CLASS, even among patients not taking aspirin, there was no statistical difference between Celebrex and NSAIDs on thromboembolic events.
- Celebrex also showed statistical superiority vs. the NSAIDs on measurements of bleeding, showing less anemia and implying less mucosal injury and less sub-clinical bleeding.
- Celebrex also showed statistical superiority to diclofenac (i.e. Voltaren) in liver safety (all hepatic events) and statistical superiority to Ibuprofen (i.e. Motrin, et al) in kidney safety (i.e. all renal events).

It appears that neither the VIGOR study on Merck's Vioxx (see March 28, 2000 FirstCall note) nor this CLASS study on Celebrex is completely void of controversy. Although no data has been presented on VIGOR, Merck has announced that Vioxx significantly reduced serious GI events (we assume that means statistical significance on all GI endpoints); however, Vioxx showed a statistical disadvantage on thromboembolic events. While Celebrex showed no disadvantage on thromboembolic events, it narrowly failed to show statistical significance on the primary GI endpoint, while it did demonstrate statistical advantage an a variety of other GI endpoints. In our view, the Celebrex "controversy" is of lessor concern as the ability to exclude the aspirin-using population, and then clearly demonstrate statistical GI superiority offers compelling evidence that this is an "aspirin issue". For Vioxx, although medical intuition implies the thromboembolic event issue is an "NSAID-issue," the theoretical cardiovascular protective benefits of Naprosyn (the VIGOR comparitor NSAID) have not been clinically proven, and the non-aspirin using cut of CLASS did not show

Additional information is available upon request.

the same problem for Celebrex. In our view, the GI superiority of both Celebrex, and Vioxx is the primary issue and should be evident to the FDA. We expect meaningful modification of the standard NSAID GI warning for both products after these data are reviewed. Although there may be some disappointment in the market on Celebrex's failure on the primary endpoint, we do not expect this to be a significant problem and would view any PHA sell-off as a buying opportunity. **PHA enjoys the greatest potential earnings growth horsepower from their COX-2 franchise. We rate PHA, PFE, and Warner Lambert (WLA/S104) as Buys, and we rate MRK a Market Performer.**

DETAILS:

In somewhat of a surprise move, summary results of the CLASS trial, the large GI outcomes trial comparing Celebrex to NSAIDs was presented by a lead investigator, Fred Silverstein MD (University of Washington) on Saturday night, April 15 at the American College of Physicians meeting in Philadelphia which we attended. Results from this trial were widely anticipated to first be presented at the Digestive Week Meeting in San Diego on May 21-24.

This trial was designed to prove the GI safety of Celebrex versus NSAIDs by demonstrating a lower incidence of severe GI events. The trial included 8,000 patients: 4,000 patients on Celebrex (dosed 400 mg, two times a day – which is double the RA dose); 2,000 patients on diclofenac (Novartis' Voltaren, dosed 75 mg, two times a day); and 2,000 on ibuprofen (dosed at 800 mg, three times a day). Average age was 59-61years in the three groups, 72% of the patients had osteoarthritis (OA) and 28% had rheumatoid arthritis (RA); 68-71% were female.

GI Safety: Patients were randomized to one of the three groups described above. Patients with lab tests implying a gastric problem (i.e. anemia) or GI symptom of sufficient suspicion were endoscoped for GI diagnosis. These endoscopies were then blinded and independently categorized by experts first as confirmed "ulcers," and, if more severe "complications" were present were further categorized into three types of complications - perforations, gastric outlet obstructions, or bleeds. Two endpoints used to measure GI safety were patients with (a)"ulcers *and* complications;" and (b) patients only with the more severe "complications." "Complications" are an especially tough clinical hurdle to show superiority on because of trial design. This is because patients with an "ulcer" that do not have "complications" are removed from the trial and therefore unable to progress to "complications." In addition, patients were allowed in this trial even if they were taking low dose aspirin (defined as up to 325-mg daily) for cardiovascular risk reduction. However, aspirin carries a GI risk of its own, in fact, though data were not presented we were told the risk of aspirin therapy alone appeared equivalent to the risk of NSAID therapy alone. The effect of aspirin on the trial may have been greater than anticipated. In addition, 10-12% of patients were initially expected to be on aspirin – the actual figure was 22%. Table 1 below shows the results on GI outcomes. For the endpoint "ulcers and complications" – Celebrex was statistically superior, both in the group including background aspirin therapy and when those patients are excluded. However, for the higher hurdle, "complications" only, Celebrex was only statistically superior when the aspirin takers were excluded, narrowly missing statistical significance (p=0.09 vs. the required p=0.05) among the study's total population. Unfortunately, this was the predefined "primary endpoint" of the trial.

Table 1: GI Outcomes from CLASS Trial

GI Outcome:	Celebrex	NSAIDs	P value
For all patients:			
Ulcers and complications	2.0%	3.5%	0.03
Complications	0.7%	1.5%	0.09
Excluding Aspirin patients:			
Ulcers and complications	1.4%	3.0%	0.02
Complications	0.4%	1.4%	0.037

Source: Fred Silverstein MD Presentation of CLASS Trial Results on 4/15/00.

Cardiovascular Safety: Given the somewhat surprising result in Merck's VIGOR trial with Vioxx showing greater cardiovascular events in the Vioxx group, the issue of Celebrex' cardiovascular safety is of increased importance. Celebrex did not show a statistical difference from NSAIDs on any of the cardiovascular measurements (see Table 2 below). This may have been due to the protective benefits to high CV risk patients which were on aspirin (which was not allowed in the Vioxx trial); however, even in the non-aspirin taking CLASS population there was no statistical difference in cardiovascular events. This may be an important advantage for Celebrex.

Table 2: Cardiovascular Outcomes from CLASS Trial*

CV Outcome:	Celebrex	Diclofenac	Ibuprofen
Any Myocardial event	1.7%	1.1%	1.3%
Myocardial infarction	0.5%	0.3%	0.5%
Any vascular event	1.4%	1.5%	1.5%
Cerebrovascular events	0.2%	0.5%*	0.5%*
Cardiovascular Deaths	0.3%	0.4%	0.5%

* Indicates statistical difference from Celebrex
Source: Fred Silverstein MD Presentation of CLASS Trial Results on 4/15/00.

Other Outcomes: Possible Celebrex Advantages on Bleeding (vs. both NSAIDs), Kidney (vs. ibuprofen) and Liver (vs. diclofenac): Table 3 profiles several other safety highlights for Celebrex. Perhaps most surprising are the apparent advantages relative to bleeding risk. Here the endpoint measurement was a decrease in the hematocrit (an anemia measure) of 10 percentage points or more or a decrease in measured hemoglobin of 2 mg/dl. Celebrex was statistically better than the NSAIDs, implying according to Dr. Silverstein less mucosal injury, and possibly less bleeding in the small intestine and bowel. On all hepatic events Celebrex was statistically superior to diclofenac (known to be tough on the liver), and on all renal events Celebrex was statistically superior to ibuprofen (known to be tough on the kidney).

Table 3: Other Outcomes from CLASS Trial*

	Celebrex	Diclofenac	Ibuprofen
"Bleeding" – HCT decrease of 10% or Hgb decrease of 2mg/dl	2.0%	4.5%*	5.0%*
All Hepatic Events (Liver)	1.9%	6.9%*	1.9%
All Renal Events (Kidney)	6.5%	6.5%	9.8%*

* Indicates statistical difference from Celebrex
Source: Fred Silverstein MD Presentation of CLASS Trial Results on 4/15/00.

(J.P. Morgan Securities Inc. acted as co- or lead-manager in an offering of securities for MRK, PHA, and WLA within the past three years. A director of J.P. Morgan is a director of MRK. The analyst or research associate holds a position in PFE and WLA.)

EXHIBIT 7

FDC REPORTS "The Pink Sheet"
PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

April 24, 2000
Volume 62 | Number 017 | page 11

Searle To Discuss Adding Celebrex 13-Month Safety Data To Label With FDA

Searle plans to approach FDA with data from a 13-month trial comparing the ulcer incidence for Celebrex to other nonsteroidal anti-inflammatory drugs, seeking a label change for the COX-2 inhibitor.

"We really believe that the data are sufficiently compelling to warrant discussions with the FDA," Searle VP-Arthritis Drug Clinical Development Steve Geis said during an April 17 conference call.

"It's hard to speculate about what the outcome of that would be. We think the data are the type of data that we have heard that the medical community and the FDA have asked for and so we just have to bring them forward and begin to talk about what are the implications," Geis said.

The Celebrex label currently contains a class warning about gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs, although it notes that "it is unclear" how the rates of GI adverse events in NSAIDs apply to Celebrex.

Celebrex labeling also suggests a need for "prospective, long-term studies" comparing the incidence of gastrointestinal adverse events "in patients taking Celebrex vs. comparator NSAID products."

Searle is likely to try to use the data from this trial to make a case for modifying or dropping the gastrointestinal warning from labeling.

Merck also claims to have preliminary data from the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, showing that its COX-2 inhibitor given at a dose of 50 mg once daily reduced the incidence of serious gastrointestinal events compared to patients treated with naproxen 500 mg twice daily.

Merck plans to submit the information to FDA and regulatory agencies worldwide in the next few months. The VIGOR study was conducted in 8,000 patients with

rheumatoid arthritis. Vioxx is currently approved for relief of osteoarthritis symptoms.

The 13-month double-blind Celebrex trial in approximately 8,000 patients compared adverse events in patients taking 400 mg of celecoxib twice daily versus patients taking 75 mg diclofenac twice daily and 800 mg ibuprofen three times daily.

Although the recommended dose of Celebrex is 200 mg daily, Searle said the company chose to study a higher dose to prove the compound's safety conclusively.

The average patient age was 60, and 70% had osteoarthritis. Some patients had significant risk factors, including a history of bleeding and ulcers and cardiovascular disease.

Data from the first six months of the trial were used for the head-to-head comparison of NSAIDs because patients were not required to remain on their assigned drug after the six months, study investigator Fred Silverstein, MD, University of Washington, explained.

At six months, the rate of serious ulcer complications, including bleeding ulcers, perforations and obstructions was .8% for the celecoxib group, compared to 1.5% in the traditional NSAID group.

While the incidence of complications was cut in half, the difference was not statistically significant, with a p-value of .09. Rate of serious ulcer complications was the primary endpoint of the study. "The issue here is you are dealing with relatively small numbers of people so it did not reach a significant level of .05," Silverstein explained.

However, when the rate of symptomatic ulcers was included in the analysis, the combined rate for celecoxib was 2% versus 3.5% for the traditional NSAID group, a statistically significant difference. Patients were considered to have symptomatic ulcers if they presented with symptoms, were endoscoped, found to have an ulcer, and taken off study, but did not develop serious ulcer complications.

Searle conducted another analysis that sought to exclude gastrointestinal complications from concomitant use of low-dose aspirin (325 mg or less), which is associated with a risk of bleeding. About 22% of patients in the study were on low-dose aspirin, commonly used as a daily preventative for myocardial infarction and stroke.

In the aspirin-free analysis, the incidence of complications was .4% for celecoxib and 1.3% for the NSAIDs, a statistically significant difference. The combined analysis of complications plus symptomatic ulcers was also statistically significant, with 1.5% of celecoxib patients developing a complication or symptomatic ulcer compared to 3% of NSAID users.

Patients on Celebrex also were less likely to experience a significant drop in blood volume than those on diclofenac or ibuprofen, with 2% of Celebrex patients experiencing a drop in hematocrit, compared to 4.5% of patients on NSAIDs.

The safety study generally confirmed the three-month gastrointestinal studies in Celebrex labeling, Lee Simon, MD, Harvard Medical School, said. The shorter-term studies in labeling assessed the prevalence of endoscopic ulcers rather than clinically serious upper GI events.

"This data set, because it demonstrates that the incidence of complications of bleeding, perforations and obstructions without the aspirin overlay was very similar to the background [rate] of .4%...begins to suggest that what we had predicted by endoscopic evaluation was truly shown in these outcome trials," he asserted.

The study also compared renal toxicity associated with Celebrex and with the two traditional NSAIDs.

Andrew Whelton, MD, Johns Hopkins University School of Medicine, explained that the most common side effect associated with NSAIDs is fluid retention leading to generalized or peripheral edema, which may destabilize blood pressure control in patients treated with hypertensives.

Less fluid and electrolyte retention was seen in Celebrex patients than in ibuprofen patients, Whelton said, while "there was significantly more problems with hypertension in ibuprofen treated patients."

An analysis of the effects of NSAIDs on kidney function determined that there were more increases in serum creatinine in diclofenac patients than in celecoxib or ibuprofen patients, Whelton noted.

In addition, diclofenac patients had more liver function abnormalities, which were measured by blood chemistry determinations of liver enzymes, Geis said.

Geis also noted that thromboembolic events were not greater in the Celebrex patients compared to NSAIDs, which are considered to have antiplatelet activity.

In Merck's study of Vioxx, the rate of thromboembolic events for the COX-2 patients was higher than that for naproxen patients.

As a result, Merck notified Vioxx investigators, and those studying its investigational COX-2 agent MK-663, of protocol amendments to allow the addition of low-dose aspirin to block platelet aggregation. Patients using low-dose aspirin were excluded from the Vioxx GI outcomes study.

One adverse event that was higher for Celebrex than the NSAIDs was skin rash. Skin rash was "somewhat higher with Celebrex than with the traditional NSAIDs, but these were minor in severity and did not cause significant problems to the patients," Geis said.

Searle plans to conduct a pharmacoeconomic analysis of data obtained in the study, in an effort to demonstrate that Celebrex' better safety profile makes it more cost-effective.

One would expect Celebrex to lower costs because of a reduced number number of ulcer complications resulting in fewer hospitalizations, Geis maintained. Celebrex' better safety profile would mean fewer workups for patients presenting with anemia, and fewer blood tests required to assess renal toxicity and liver functioning, he added.

Silverstein agreed that the lower incidence of hematocrit drops among Celebrex patients would mean that fewer patients would require colonoscopies, which are used to rule out the possibility of colon cancer when older patients present with anemia.

"If you have a 1% or 2% lowering of the incidence of hematocrit drop you could be reducing the number of workups to rule out colon cancer by 100,000 or 200,000 and that workup is usually a few thousand dollars to do a colonoscopy" and other tests, he said.

Removal of the NSAID class warning from Celebrex labeling could facilitate promotions differentiating the drug from the class.

On April 6, Searle received a letter from FDA's ad division concerning a "homemade" promotional piece that "misleadingly suggests that Celebrex is safer than Relafen because the PI for Celebrex does not contain standard NSAID class labeling."

FDA also cautioned Searle about suggesting that Celebrex may be used in Coumadin patients while Vioxx is contraindicated in that group. The PIs for Celebrex and Vioxx "both state that anticoagulant activity should be monitored" when therapy is initiated, FDA pointed out ([1]see following story).

EXHIBIT 8

PR Newswire

May 23, 2000, Tuesday

SECTION: FINANCIAL NEWS

DISTRIBUTION: TO BUSINESS AND MEDICAL EDITORS

LENGTH: 1522 words

HEADLINE: Findings from Celebrex(R) Safety Study Show Traditional NSAID Comparators Can Cause Serious GI Complications Within First Few Days of Treatment;

No Increased Risk of GI Complications Observed for H. Pylori Positive Patients on Celebrex

DATELINE: SAN DIEGO, May 23

BODY:

New data from the Celebrex(R) (celecoxib capsules) long-term safety study presented during Digestive Disease Week (DDW) revealed that the risk for serious gastrointestinal complications with the NSAID comparators ibuprofen and diclofenac can start within the first few days after treatment begins. Further, study patients who were H. pylori positive had a two times greater risk of developing both symptomatic ulcers and ulcer complications when taking the NSAID comparators than did H. pylori negative patients. No such increase was observed with patients taking Celebrex, regardless of H. pylori status.

"This study reinforces what gastroenterologists have always suspected -- that even short-term therapy carries risks. Many physicians feel that patients requiring short-term administration of traditional NSAIDs are not at risk for a serious gastrointestinal event. These results tell a different story, highlighting that many of the events caused by traditional NSAIDs occurred within the first few weeks," said Jay Goldstein, MD, Associate Professor of

Medicine at the University of Illinois at Chicago and Chairman of the GI Events committee of the Celebrex long-term arthritis safety study, who presented the findings at a satellite symposium sponsored by Searle and Pfizer Inc during DDW.

The Celebrex long-term arthritis safety study, an approximately 13-month, multi-center, randomized, double-blind outcomes trial of about 8,000 arthritis patients -- 5,800 with osteoarthritis (OA) and 2,200 with rheumatoid arthritis (RA) -- was designed to mirror everyday clinical practice by enrolling a broad spectrum of patients, including adult patients of all ages and disease severity, and patients taking low-dose aspirin for cardioprotection. The study, designed to obtain a rigorous assessment of Celebrex safety, compared four times the recommended OA dose of Celebrex (800 mg daily) to typical daily doses of ibuprofen (2400 mg daily) and diclofenac (150 mg daily). The Celebrex study dose is twice the highest recommended RA dose.

Impact on Required Medical Care Studied

Under the real-world conditions of the study, significant decreases in the use of medical resources were shown in the Celebrex group versus the other NSAIDs studied. On four times the recommended Celebrex OA dose, 12.6 percent of patients required office visits for blood work and evaluation versus 16 percent of patients on usual doses of the NSAID comparators; approximately twenty percent of each group were referred to a specialist, most requiring endoscopy and a complex medical work-up. This amounted to 25 percent fewer office visits and complex work-ups for patients taking Celebrex. "This is an important finding with respect to the increased burden on our medical system and the healthcare resources needed to treat these patients - especially given the finding that serious complications can occur early in treatment," noted Dr. Goldstein.

New Treatment Withdrawal Findings

Withdrawal from the study due to GI symptoms for patients on Celebrex versus traditional NSAIDs was also assessed in the trial. Tolerability data were presented that indicate diclofenac patients had a more difficult time remaining on treatment due to increases in moderate to severe GI symptoms. Significantly more patients on diclofenac were forced to withdraw from treatment as a result of these side effects, as compared with patients on Celebrex. Additionally, significantly more patients on ibuprofen than on Celebrex were forced to withdraw from treatment due to lack of efficacy. These data highlight that arthritis patients need both efficacy and tolerability from their therapy in order to stay with treatment.

Blood Loss Data Have Broad Implications

As reported at the symposium, study data show that there was an increased incidence of blood loss -- equivalent to two pints or more - among patients on the NSAID comparators versus Celebrex, even among those without bleeding ulcers. The rate of blood loss with the NSAID comparators was 5.0 percent, and with Celebrex was 2.4 percent. In the original Celebrex clinical trials, the rate of blood loss with placebo was 1.6 percent.

"Importantly, the lower incidence of GI blood loss has implications for a patient's overall health," Dr. Goldstein noted. Chronic GI blood loss, which often goes undetected, can result in anemia. Less total blood in the body means less oxygen is circulating through the body. To compensate, a patient's heart must work harder and faster to pump more blood through the system. Left untreated, anemia can exacerbate underlying coronary artery disease and precipitate heart attacks and heart failure.

According to Dr. Goldstein, "Blood loss of this kind is often difficult to pinpoint. When discovered, however, patients may be forced to discontinue treatment, thereby preventing them from getting effective relief from their

arthritis symptoms. Obviously we'd prefer to avoid such an outcome."

Cardiovascular Findings

The long-term safety study also indicated that four times the recommended OA dose of Celebrex, taken with or without aspirin, posed no increased risk of heart attacks or strokes compared with ibuprofen and diclofenac. Approximately 70 percent of the aspirin group and 50 percent of non-aspirin users had cardiovascular risk factors such as hypertension, high cholesterol, tobacco use and a history of heart attacks.

Among study participants not taking aspirin, the incidence of heart attack for Celebrex was 0.2 percent, and 0.1 percent for the NSAID comparators. For the same group of patients, the incidence of stroke was less than 0.1 percent for Celebrex, and 0.3 percent for the NSAID comparators. Among study participants taking aspirin, the incidence of heart attack for Celebrex was 0.5 percent, and 0.4 percent for the NSAID comparators. For the same group of patients, the incidence of stroke was 0.2 percent for Celebrex and 0.5 percent for the NSAID comparators. None of the differences were statistically significant. Celebrex is not a substitute for low-dose aspirin used for cardioprotection.

Aspirin: An Independent Risk Factor for Ulcers

Among non-aspirin users, patients on Celebrex taking four times the recommended dose for OA experienced significantly fewer ulcer complications compared with ibuprofen and diclofenac. Patients who needed aspirin were allowed to participate in this study since a large number of patients with arthritis take low-dose aspirin for cardioprotection, as did one-in-five patients in this study. Excluding aspirin patients from the analysis, however, offers a clearer picture of the impact of Celebrex on GI safety since aspirin is an independent risk factor for GI complications. These patients experienced

three-fold fewer (64 percent) ulcer complications, a statistically significant difference from the NSAID comparators. When patients taking aspirin for cardioprotection were added to the analysis, those on Celebrex experienced two-fold fewer ulcer complications versus the traditional NSAID comparators, narrowly missing statistical significance.

Patients who have a known allergic reaction to celecoxib, certain sulfa drugs called sulfonamides, aspirin or NSAIDs, or who are in their third trimester of pregnancy should not use Celebrex. As with all NSAIDs, serious GI tract ulcerations can occur without warning symptoms. Physicians and patients should remain alert to the signs and symptoms of GI bleeding. As with all NSAIDs, Celebrex should be used with caution in patients with fluid retention, hypertension, or heart failure. The most common side effects of Celebrex were dyspepsia, diarrhea and abdominal pain, which were generally mild to moderate.

Celebrex is co-promoted by Searle, now part of Pharmacia Corporation, and Pfizer Inc. Pharmacia Corporation (NYSE: PHA) is a leading global pharmaceutical company created through the merger of Pharmacia & Upjohn with Monsanto Company and its G.D. Searle unit. Pharmacia has a broad product portfolio, a robust pipeline of new medicines, and an annual investment of more than $2 billion in pharmaceutical research and development.

Pfizer Inc (NYSE: PFE) is a research-based, global pharmaceutical company that discovers, develops, manufactures and markets innovative medicines for humans and animals. The company reported revenues of more than $16 billion in 1999 and expects to spend about $3.2 billion on research and development this year. For more information on Pfizer, access http://www.pfizer.com.

For complete prescribing information on Celebrex, access http://www.celebrex.com or call toll-free 888-735-3214.

SOURCE Pharmacia Corporation and Pfizer Inc

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